

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 March 2002 (21.03.2002)

PCT

(10) International Publication Number
WO 02/22607 A1

(51) International Patent Classification⁷: **C07D 403/12**, 401/14, A61K 31/506, 31/4155, A61P 35/00, C07D 403/14, 405/14, 409/14, 471/04, 487/04, 401/12, 493/04, 498/04, 513/04

Albert [US/US]; 123 Orchard Street, Apartment 36, Somerville, MA 02144 (US). KAY, David [GB/GB]; 4 Church Path, Purton, Purton, Wiltshire 02144 (GB).

(21) International Application Number: PCT/US01/28940

(74) Agents: SILVERMAN, Ian et al.; Vertex Pharmaceuticals Inc., 130 Waverly Street, Cambridge, MA 02139-4242 (US).

(22) International Filing Date:

14 September 2001 (14.09.2001)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/232,795	15 September 2000 (15.09.2000)	US
60/257,887	21 December 2000 (21.12.2000)	US
60/286,949	27 April 2001 (27.04.2001)	US

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **VERTEX PHARMACEUTICALS INCORPORATED** [US/US]; Patent Department, 130 Waverly Street, Cambridge, MA 02139-4242 (US).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- entirely in electronic form (except for this front page) and available upon request from the International Bureau

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 02/22607 A1

(54) Title: PYRAZOLE COMPOUNDS USEFUL AS PROTEIN KINASE INHIBITORS

(57) **Abstract:** This invention describes novel pyrazole compounds of formula II: wherein Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1, 2, 4-triazinyl ring, and R², R², R^x, and R^y are as described in the specification. Ring C has an ortho substituent and is optionally substituted in the non-ortho positions. R² and R² are optionally taken together with their intervening atoms to form a fused ring system, such as an indazole ring; and R^x and R^y are optionally taken together with their intervening atoms to form a fused ring system, such as a quinazoline ring. The compounds are useful as protein kinase inhibitors, especially as inhibitors of GSK-3, for treating diseases such as diabetes and Alzheimer's disease.

PYRAZOLE COMPOUNDS USEFUL AS PROTEIN KINASE INHIBITORSCROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to US
Provisional Patent Application 60/232,795 filed September
15, 2000, US Provisional Patent Application 60/257,887
filed December 21, 2000 and US Provisional Patent
5 Application 60/286,949 filed April 27, 2001, the contents
of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention is in the field of
medicinal chemistry and relates to compounds that are
protein kinase inhibitors, compositions containing such
10 compounds and methods of use. More particularly, this
invention relates to compounds that are inhibitors of
GSK-3 and Aurora-2 protein kinases. The invention also
relates to methods of treating diseases associated with
these protein kinases, such as diabetes, cancer and
15 Alzheimer's disease.

BACKGROUND OF THE INVENTION

The search for new therapeutic agents has been
greatly aided in recent years by better understanding of
20 the structure of enzymes and other biomolecules
associated with target diseases. One important class of
enzymes that has been the subject of extensive study is
the protein kinases.

Protein kinases mediate intracellular signal
25 transduction. They do this by effecting a phosphoryl
transfer from a nucleoside triphosphate to a protein
acceptor that is involved in a signaling pathway. There

are a number of kinases and pathways through which extracellular and other stimuli cause a variety of cellular responses to occur inside the cell. Examples of such stimuli include environmental and chemical stress signals (e.g. osmotic shock, heat shock, ultraviolet radiation, bacterial endotoxin, H₂O₂), cytokines (e.g. interleukin-1 (IL-1) and tumor necrosis factor α (TNF- α)), and growth factors (e.g. granulocyte macrophage-colony-stimulating factor (GM-CSF), and fibroblast growth factor (FGF)). An extracellular stimulus may effect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis and regulation of cell cycle.

Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include autoimmune diseases, inflammatory diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease or hormone-related diseases. Accordingly, there has been a substantial effort in medicinal chemistry to find protein kinase inhibitors that are effective as therapeutic agents.

Aurora-2 is a serine/threonine protein kinase that has been implicated in human cancer, such as colon, breast and other solid tumors. This kinase is believed to be involved in protein phosphorylation events that regulate the cell cycle. Specifically, Aurora-2 may play a role in controlling the accurate segregation of chromosomes during mitosis. Misregulation of the cell cycle can lead to cellular proliferation and other abnormalities. In human colon cancer tissue, the aurora-

2 protein has been found to be overexpressed. See Bischoff et al., *EMBO J.*, 1998, 17, 3052-3065; Schumacher et al., *J. Cell Biol.*, 1998, 143, 1635-1646; Kimura et al., *J. Biol. Chem.*, 1997, 272, 13766-13771.

5 Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase comprised of α and β isoforms that are each encoded by distinct genes [Coghlan et al., *Chemistry & Biology*, 7, 793-803 (2000); Kim and Kimmel, *Curr. Opinion Genetics Dev.*, 10, 508-514 (2000)].
10 GSK-3 has been implicated in various diseases including diabetes, Alzheimer's disease, CNS disorders such as manic depressive disorder and neurodegenerative diseases, and cardiomyocyte hypertrophy [WO 99/65897; WO 00/38675; and Haq et al., *J. Cell Biol.* (2000) 151, 117]. These
15 diseases may be caused by, or result in, the abnormal operation of certain cell signaling pathways in which GSK-3 plays a role. GSK-3 has been found to phosphorylate and modulate the activity of a number of regulatory proteins. These proteins include glycogen
20 synthase which is the rate limiting enzyme necessary for glycogen synthesis, the microtubule associated protein Tau, the gene transcription factor β -catenin, the translation initiation factor eIF2B, as well as ATP citrate lyase, axin, heat shock factor-1, c-Jun, c-Myc,
25 c-Myb, CREB, and CEPBa. These diverse protein targets implicate GSK-3 in many aspects of cellular metabolism, proliferation, differentiation and development.

 In a GSK-3 mediated pathway that is relevant for the treatment of type II diabetes, insulin-induced
30 signaling leads to cellular glucose uptake and glycogen synthesis. Along this pathway, GSK-3 is a negative regulator of the insulin-induced signal. Normally, the presence of insulin causes inhibition of GSK-3 mediated

phosphorylation and deactivation of glycogen synthase. The inhibition of GSK-3 leads to increased glycogen synthesis and glucose uptake [Klein et al., *PNAS*, 93, 8455-9 (1996); Cross et al., *Biochem. J.*, 303, 21-26 (1994); Cohen, *Biochem. Soc. Trans.*, 21, 555-567 (1993); Massillon et al., *Biochem J.* 299, 123-128 (1994)].

However, in a diabetic patient where the insulin response is impaired, glycogen synthesis and glucose uptake fail to increase despite the presence of relatively high blood levels of insulin. This leads to abnormally high blood levels of glucose with acute and long term effects that may ultimately result in cardiovascular disease, renal failure and blindness. In such patients, the normal insulin-induced inhibition of GSK-3 fails to occur. It has also been reported that in patients with type II diabetes, GSK-3 is overexpressed [WO 00/38675]. Therapeutic inhibitors of GSK-3 are therefore potentially useful for treating diabetic patients suffering from an impaired response to insulin.

GSK-3 activity has also been associated with Alzheimer's disease. This disease is characterized by the well-known β -amyloid peptide and the formation of intracellular neurofibrillary tangles. The neurofibrillary tangles contain hyperphosphorylated Tau protein where Tau is phosphorylated on abnormal sites. GSK-3 has been shown to phosphorylate these abnormal sites in cell and animal models. Furthermore, inhibition of GSK-3 has been shown to prevent hyperphosphorylation of Tau in cells [Lovestone et al., *Current Biology* 4, 1077-86 (1994); Brownlees et al., *Neuroreport* 8, 3251-55 (1997)]. Therefore, it is believed that GSK-3 activity may promote generation of the neurofibrillary tangles and the progression of Alzheimer's disease.

Another substrate of GSK-3 is β -catenin which is degraded after phosphorylation by GSK-3. Reduced levels of β -catenin have been reported in schizophrenic patients and have also been associated with other 5 diseases related to increase in neuronal cell death [Zhong et al., *Nature*, 395, 698-702 (1998); Takashima et al., *PNAS*, 90, 7789-93 (1993); Pei et al., *J. Neuropathol. Exp.*, 56, 70-78 (1997)].

As a result of the biological importance of 10 GSK-3, there is current interest in therapeutically effective GSK-3 inhibitors. Small molecules that inhibit GSK-3 have recently been reported [WO 99/65897 (Chiron) and WO 00/38675 (SmithKline Beecham)].

For many of the aforementioned diseases 15 associated with abnormal GSK-3 activity, other protein kinases have also been targeted for treating the same diseases. However, the various protein kinases often act through different biological pathways. For example, certain quinazoline derivatives have been reported 20 recently as inhibitors of p38 kinase (WO 00/12497 to Scios). The compounds are reported to be useful for treating conditions characterized by enhanced p38- α activity and/or enhanced TGF- β activity. While p38 activity has been implicated in a wide variety of 25 diseases, including diabetes, p38 kinase is not reported to be a constituent of an insulin signaling pathway that regulates glycogen synthesis or glucose uptake. Therefore, unlike GSK-3, p38 inhibition would not be expected to enhance glycogen synthesis and/or glucose 30 uptake.

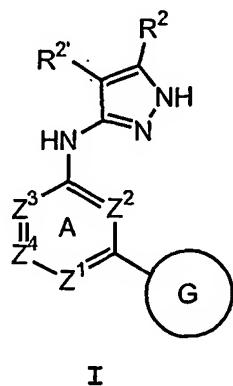
There is a continued need to find new therapeutic agents to treat human diseases. The protein kinases aurora-2 and GSK-3 are especially attractive

targets for the discovery of new therapeutics due to their important role in cancer, diabetes, Alzheimer's disease and other diseases.

5

DESCRIPTION OF THE INVENTION

It has now been found that compounds of this invention and pharmaceutical compositions thereof are effective as protein kinase inhibitors, particularly as inhibitors of aurora-2 and GSK-3. These compounds have 10 the general formula I:



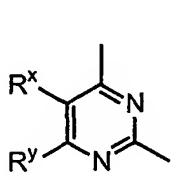
I

15 or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

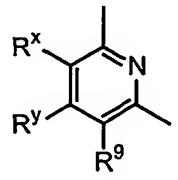
Z¹ to Z⁴ are as described below;

Ring A is selected from the group consisting of:

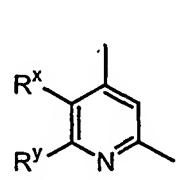
20



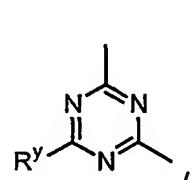
a



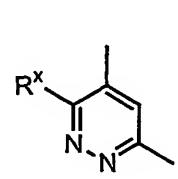
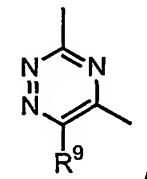
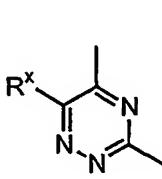
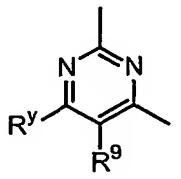
b



c



d

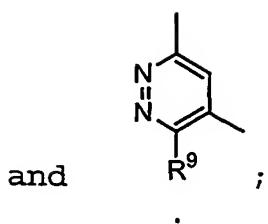


e

f

g

h



5

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C has one or two ortho substituents independently selected from -R¹, any substitutable non-ortho carbon position on Ring C is independently substituted by -R⁵, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or -R⁸;

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or -R⁵, and at any substitutable ring nitrogen by -R⁴, provided that when Ring D is a six-membered aryl or heteroaryl ring, -R⁵ is hydrogen at each ortho carbon position of Ring D;

R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl,

and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or -R⁸, said C₁₋₆ aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R¹

5 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

R^x and R^y are independently selected from T-R³, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or T-R³, and any substitutable nitrogen on said ring formed by R^x and R^y is substituted by R⁴;

T is a valence bond or a C₁₋₄ alkylidene chain;

R² and R^{2'} are independently selected from -R, -T-W-R⁶, or R² and R^{2'} are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R² and R^{2'} is substituted by halo, oxo, -CN, -NO₂, -R⁷, or -V-R⁶, and any substitutable nitrogen on said ring formed by R² and R^{2'} is substituted by R⁴;

10 R³ is selected from -R, -halo, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)CO₂ (optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁷)₂;

15 each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆

aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷; or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

5 each R⁵ is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂ (optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂,

10 -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, or R⁵ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;

each R⁶ is independently selected from hydrogen or an optionally substituted C₁₋₄ aliphatic group, or two R⁶ groups on the same nitrogen atom are taken together

with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;
each R⁷ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring;

5 each R⁸ is independently selected from an optionally substituted C₁₋₄ aliphatic group, -OR⁶, -SR⁶, -COR⁶, -SO₂R⁶, -N(R⁶)₂, -N(R⁶)N(R⁶)₂, -CN, -NO₂, -CON(R⁶)₂, or 10 -CO₂R⁶; and

R⁹ is selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, 15 -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂.

As used herein, the following definitions shall apply unless otherwise indicated. The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted" or with the term "(un)substituted." Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

The term "aliphatic" as used herein means straight-chain, branched or cyclic C_{1-C₁₂} hydrocarbons which are completely saturated or which contain one or more units of unsaturation but which are not aromatic.

30 For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or

(cycloalkyl) alkenyl. The terms "alkyl", "alkoxy", "hydroxyalkyl", "alkoxyalkyl", and "alkoxycarbonyl", used alone or as part of a larger moiety includes both straight and branched chains containing one to twelve carbon atoms. The terms "alkenyl" and "alkynyl" used alone or as part of a larger moiety shall include both straight and branched chains containing two to twelve carbon atoms. The term "cycloalkyl" used alone or as part of a larger moiety shall include cyclic C₃-C₁₂ hydrocarbons which are completely saturated or which contain one or more units of unsaturation, but which are not aromatic.

The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I.

The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl).

The terms "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic" as used herein means an aliphatic ring system having three to fourteen members. The terms "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic" whether saturated or partially unsaturated, also refers to rings that are optionally substituted. The terms "carbocycle", "carbocyclyl", "carbocyclo", or

"carbocyclic" also include aliphatic rings that are fused to one or more aromatic or nonaromatic rings, such as in a decahydronaphthyl or tetrahydronaphthyl, where the radical or point of attachment is on the aliphatic ring.

5 The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to aromatic ring groups having five to fourteen members, such as phenyl, benzyl, phenethyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. The term "aryl" also refers to rings that are 10 optionally substituted. The term "aryl" may be used interchangeably with the term "aryl ring". "Aryl" also includes fused polycyclic aromatic ring systems in which an aromatic ring is fused to one or more rings. Examples 15 include 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. Also included within the scope of the term "aryl", as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as in an indanyl, phenanthridinyl, or 20 tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring.

The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein includes non-aromatic ring systems having five to fourteen members, preferably five to ten, in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, or S. Examples of heterocyclic rings include 3-1H-benzimidazol-2-one, (1-substituted)-2-oxo-benzimidazol-3-yl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, [1,3]-dioxalanyl, [1,3]-dithiolanyl, [1,3]-dioxanyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholinyl, 3-morpholinyl, 4-

morpholinyl, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl,
5 4-thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-phthalimidinyl, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, benzothiolanyl, and benzothianyl. Also included within the scope of the term "heterocyclyl" or "heterocyclic", as it is used herein, 10 is a group in which a non-aromatic heteroatom-containing ring is fused to one or more aromatic or non-aromatic rings, such as in an indolinyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the non-aromatic 15 heteroatom-containing ring. The term "heterocycle", "heterocyclyl", or "heterocyclic" whether saturated or partially unsaturated, also refers to rings that are optionally substituted.

The term "heteroaryl", used alone or as part of 20 a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to heteroaromatic ring groups having five to fourteen members. Examples of heteroaryl rings include 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-tetrazolyl, 2-triazolyl, 5-triazolyl, 2-thienyl, 3-thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, indolyl,

isoindolyl, acridinyl, or benzoisoxazolyl. Also included within the scope of the term "heteroaryl", as it is used herein, is a group in which a heteroatomic ring is fused to one or more aromatic or nonaromatic rings where the radical or point of attachment is on the heteroaromatic ring. Examples include tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[3,4-d]pyrimidinyl. The term "heteroaryl" also refers to rings that are optionally substituted. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Examples of suitable substituents on the unsaturated carbon atom of an aryl, heteroaryl, aralkyl, or heteroaralkyl group include a halogen, -R°, -OR°, -SR°, 1,2-methylene-dioxy, 1,2-ethylenedioxy, protected OH (such as acyloxy), phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), -CH₂(Ph), substituted -CH₂(Ph), -CH₂CH₂(Ph), substituted -CH₂CH₂(Ph), -NO₂, -CN, -N(R°)₂, -NR°C(O)R°, -NR°C(O)N(R°)₂, -NR°CO₂R°, -NR°NR°C(O)R°, -NR°NR°C(O)N(R°)₂, -NR°NR°CO₂R°, -C(O)C(O)R°, -C(O)CH₂C(O)R°, -CO₂R°, -C(O)R°, -C(O)N(R°)₂, -OC(O)N(R°)₂, -S(O)₂R°, -SO₂N(R°)₂, -S(O)R°, -NR°SO₂N(R°)₂, -NR°SO₂R°, -C(=S)N(R°)₂, -C(=NH)-N(R°)₂, -(CH₂)_yNHC(O)R°, -(CH₂)_yNHC(O)CH(V-R°)(R°); wherein R° is hydrogen, a substituted or unsubstituted aliphatic group, an unsubstituted heteroaryl or heterocyclic ring, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), -CH₂(Ph), or substituted -CH₂(Ph); y is 0-6; and V is a linker group. Examples of substituents on the aliphatic

group or the phenyl ring of R° include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, 5 nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

An aliphatic group or a non-aromatic heterocyclic ring may contain one or more substituents. Examples of suitable substituents on the saturated carbon 10 of an aliphatic group or of a non-aromatic heterocyclic ring include those listed above for the unsaturated carbon of an aryl or heteroaryl group and the following: =O, =S, =NNHR*, =NN(R*)₂, =N-, =NNHC(O)R*, =NNHCO₂(alkyl), =NNHSO₂(alkyl), or =NR*, where each R* is independently 15 selected from hydrogen, an unsubstituted aliphatic group or a substituted aliphatic group. Examples of substituents on the aliphatic group include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, 20 nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

Suitable substituents on the nitrogen of a non-aromatic heterocyclic ring include -R⁺, -N(R⁺)₂, -C(O)R⁺, 25 -CO₂R⁺, -C(O)C(O)R⁺, -C(O)CH₂C(O)R⁺, -SO₂R⁺, -SO₂N(R⁺)₂, -C(=S)N(R⁺)₂, -C(=NH)-N(R⁺)₂, and -NR⁺SO₂R⁺; wherein R⁺ is hydrogen, an aliphatic group, a substituted aliphatic group, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), CH₂(Ph), substituted CH₂(Ph), 30 or an unsubstituted heteroaryl or heterocyclic ring. Examples of substituents on the aliphatic group or the phenyl ring include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl,

dialkylaminocarbonyl, alkylaminocarbonyloxy,
dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy,
alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or
haloalkyl.

5 The term "linker group" or "linker" means an organic moiety that connects two parts of a compound. Linkers are typically comprised of an atom such as oxygen or sulfur, a unit such as -NH-, -CH₂-, -C(O)-, -C(O)NH-, or a chain of atoms, such as an alkylidene chain. The
10 molecular mass of a linker is typically in the range of about 14 to 200, preferably in the range of 14 to 96 with a length of up to about six atoms. Examples of linkers include a saturated or unsaturated C₁₋₆ alkylidene chain which is optionally substituted, and wherein one or two
15 saturated carbons of the chain are optionally replaced by -C(O)-, -C(O)C(O)-, -CONH-, -CONHNH-, -CO₂-, -OC(O)-, -NHCO₂-, -O-, -NHCONH-, -OC(O)NH-, -NHNH-, -NHCO-, -S-, -SO-, -SO₂-, -NH-, -SO₂NH-, or -NHSO₂-.

20 The term "alkylidene chain" refers to an optionally substituted, straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation. The optional substituents are as described above for an aliphatic group.

25 A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature of 40 °C or less, in the absence of
30 moisture or other chemically reactive conditions, for at least a week.

 Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms

of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of
5 the invention. Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a
10 hydrogen by a deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

Compounds of formula I or salts thereof may be formulated into compositions. In a preferred embodiment,
15 the composition is a pharmaceutical composition. In one embodiment, the composition comprises an amount of the protein kinase inhibitor effective to inhibit a protein kinase, particularly GSK-3, in a biological sample or in a patient. In another embodiment, compounds of this
20 invention and pharmaceutical compositions thereof, which comprise an amount of the protein kinase inhibitor effective to treat or prevent a GSK-3-mediated condition and a pharmaceutically acceptable carrier, adjuvant, or vehicle, may be formulated for administration to a
25 patient.

The term "GSK-3-mediated condition" or "disease", as used herein, means any disease or other deleterious condition or state in which GSK-3 is known to play a role. Such diseases or conditions include,
30 without limitation, diabetes, Alzheimer's disease, Huntington's Disease, Parkinson's Disease, AIDS-associated dementia, amyotrophic lateral sclerosis (AML),

multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia, and baldness.

One aspect of this invention relates to a method of enhancing glycogen synthesis and/or lowering 5 blood levels of glucose in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof. This method is especially useful for diabetic patients. Another 10 method relates to inhibiting the production of hyperphosphorylated Tau protein, which is useful in halting or slowing the progression of Alzheimer's disease. Another method relates to inhibiting the phosphorylation of β -catenin, which is useful for 15 treating schizophrenia.

Another aspect of the invention relates to inhibiting GSK-3 activity in a biological sample, which method comprises contacting the biological sample with a GSK-3 inhibitor of formula I.

20 Another aspect of this invention relates to a method of inhibiting Aurora-2 activity in a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

25 Another aspect of this invention relates to a method of treating or preventing an Aurora-2-mediated disease with an Aurora-2 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a 30 compound of formula I or a pharmaceutical composition thereof.

The term "Aurora-2-mediated condition" or "disease", as used herein, means any disease or other

deleterious condition in which Aurora is known to play a role. The term "Aurora-2-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with an Aurora-2 inhibitor.

5 Such conditions include, without limitation, cancer. The term "cancer" includes, but is not limited to the following cancers: colon and ovarian.

Another aspect of the invention relates to inhibiting Aurora-2 activity in a biological sample, 10 which method comprises contacting the biological sample with the Aurora-2 inhibitor of formula I, or a composition thereof.

Another aspect of this invention relates to a method of treating or preventing a CDK-2-mediated 15 diseases with a CDK-2 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof.

The term "CDK-2-mediated condition" or 20 "disease", as used herein, means any disease or other deleterious condition in which CDK-2 is known to play a role. The term "CDK-2-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a CDK-2 inhibitor. Such 25 conditions include, without limitation, cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid arthritis. See Fischer, P.M. 30 and Lane, D.P., *Current Medicinal Chemistry*, 7, 1213-1245 (2000); Mani, S., Wang, C., Wu, K., Francis, R. and Pestell, R., *Exp. Opin. Invest. Drugs*, 9, 1849 (2000); Fry, D.W. and Garrett, M.D., *Current Opinion in*

Oncologic, Endocrine & Metabolic Investigational Drugs,
2, 40-59 (2000).

Another aspect of the invention relates to inhibiting CDK-2 activity in a biological sample or a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

Another aspect of this invention relates to a method of treating or preventing an ERK-2-mediated disease with an ERK-2 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof.

The term "ERK-mediated condition", as used herein means any disease state or other deleterious condition in which ERK is known to play a role. The term "ERK-2-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a ERK-2 inhibitor. Such conditions include, without limitation, cancer, stroke, diabetes, hepatomegaly, cardiovascular disease including cardiomegaly, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders including asthma, inflammation, neurological disorders and hormone-related diseases. The term "cancer" includes, but is not limited to the following cancers: breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma,

papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral),
5 lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, and leukemia. ERK-2 protein kinase and its implication in various diseases has been described [Bokemeyer et al. 1996, *Kidney Int.* 49, 1187; Anderson et
10 al., 1990, *Nature* 343, 651; Crews et al., 1992, *Science* 258, 478; Bjorbaek et al., 1995, *J. Biol. Chem.* 270, 18848; Rouse et al., 1994, *Cell* 78, 1027; Raingeaud et al., 1996, *Mol. Cell Biol.* 16, 1247; Raingeaud et al.
15 1996; Chen et al., 1993 *Proc. Natl. Acad. Sci. USA* 90, 10952; Oliver et al., 1995, *Proc. Soc. Exp. Biol. Med.* 210, 162; Moodie et al., 1993, *Science* 260, 1658; Frey and Mulder, 1997, *Cancer Res.* 57, 628; Sivaraman et al.,
1997, *J Clin. Invest.* 99, 1478; Whelchel et al., 1997,
Am. J. Respir. Cell Mol. Biol. 16, 589].

20 Another aspect of the invention relates to inhibiting ERK-2 activity in a biological sample or a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

25 Another aspect of this invention relates to a method of treating or preventing an AKT-mediated disease with an AKT inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula
30 I or a pharmaceutical composition thereof.

The term "AKT-mediated condition", as used herein, means any disease state or other deleterious condition in which AKT is known to play a role. The term

"AKT-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a AKT inhibitor. AKT-mediated diseases or conditions include, but are not limited to, proliferative disorders, cancer, and neurodegenerative disorders. The association of AKT, also known as protein kinase B, with various diseases has been described [Khwaja, A., *Nature*, pp. 33-34, 1990; Zang, Q. Y., et al, *Oncogene*, 19 2000; Kazuhiko, N., et al, *The Journal of Neuroscience*, 20 10 2000].

Another aspect of the invention relates to inhibiting AKT activity in a biological sample or a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

Another aspect of this invention relates to a method of treating or preventing a Src-mediated disease with a Src inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof.

The term "Src-mediated condition", as used herein means any disease state or other deleterious condition in which Src is known to play a role. The term "Src-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a Src inhibitor. Such conditions include, without limitation, hypercalcemia, osteoporosis, osteoarthritis, cancer, symptomatic treatment of bone metastasis, and Paget's disease. Src protein kinase and its implication in various diseases has been described [Soriano, *Cell*, 69, 551 (1992); Soriano et al., *Cell*, 64, 693 (1991); Takayanagi, *J. Clin. Invest.*, 104, 137 (1999); Boschelli,

Drugs of the Future 2000, 25(7), 717, (2000); Talamonti, J. Clin. Invest., 91, 53 (1993); Lutz, Biochem. Biophys. Res. 243, 503 (1998); Rosen, J. Biol. Chem., 261, 13754 (1986); Bolen, Proc. Natl. Acad. Sci. USA, 84, 2251 5 (1987); Masaki, Hepatology, 27, 1257 (1998); Biscardi, Adv. Cancer Res., 76, 61 (1999); Lynch, Leukemia, 7, 1416 (1993); Wiener, Clin. Cancer Res., 5, 2164 (1999); Staley, Cell Growth Diff., 8, 269 (1997)].

Another aspect of the invention relates to 10 inhibiting Src activity in a biological sample or a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

The term "pharmaceutically acceptable carrier, 15 adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that may be administered to a patient, together with a compound of this invention; and which does not destroy the pharmacological activity thereof.

20 The term "patient" includes human and veterinary subjects.

The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; preparations of an enzyme suitable for *in vitro* 25 assay; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

The amount effective to inhibit protein kinase for example, GSK-3 and Aurora-2, is one that measurably 30 inhibits the kinase activity where compared to the activity of the enzyme in the absence of an inhibitor. Any method may be used to determine inhibition, such as,

for example, the Biological Testing Examples described below.

Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but 5 are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts 10 or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium 15 carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The compositions of the present invention may be administered orally, parenterally, by inhalation 20 spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional 25 and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. 30 These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable

solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's
5 solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and
10 its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain
15 alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and
20 other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

25 The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used
30 include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When

aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

5 Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature
10 but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

15 The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

20 Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

25 For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid
30 petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or

cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, 5 cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, 10 as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

15 The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, 20 employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

In addition to the compounds of this invention, 25 pharmaceutically acceptable derivatives or prodrugs of the compounds of this invention may also be employed in compositions to treat or prevent the above-identified diseases or disorders.

A "pharmaceutically acceptable derivative or 30 prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing, either directly or

indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives or prodrugs are those that increase the bioavailability of the compounds of 5 this invention when such compounds are administered to a patient (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic 10 system) relative to the parent species.

Pharmaceutically acceptable prodrugs of the compounds of this invention include, without limitation, esters, amino acid esters, phosphate esters, metal salts and sulfonate esters.

15 Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, 20 benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, 25 hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, 30 succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in

obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

10 The amount of the protein kinase inhibitor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the patient treated and the particular mode of administration. Preferably, the compositions should be formulated so that 15 a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient 20 will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity 25 of the particular disease being treated. The amount of the inhibitor will also depend upon the particular compound in the composition.

Depending upon the particular protein kinase-mediated condition to be treated or prevented, additional 30 therapeutic agents, which are normally administered to treat or prevent that condition, may be administered together with the inhibitors of this invention. For example, in the treatment of diabetes other anti-diabetic

agents may be combined with the GSK-3 inhibitors of this invention to treat diabetes. These agents include, without limitation, insulin or insulin analogues, in injectable or inhalation form, glitazones, alpha glucosidase inhibitors, biguanides, insulin sensitizers, and sulfonyl ureas.

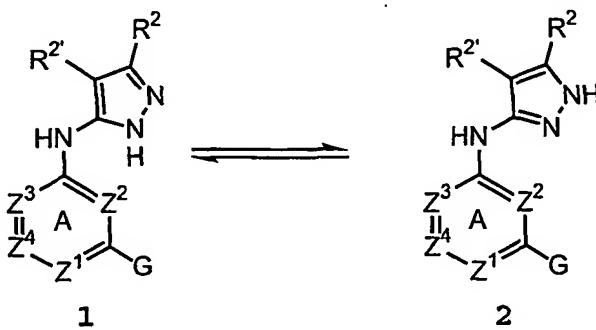
Other examples of agents the inhibitors of this invention may also be combined with include, without limitation, chemotherapeutic agents or other anti-proliferative agents such as adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

Those additional agents may be administered separately from the protein kinase inhibitor-containing composition, as part of a multiple dosage regimen.

Alternatively, those agents may be part of a single dosage form, mixed together with the protein kinase inhibitor of this invention in a single composition.

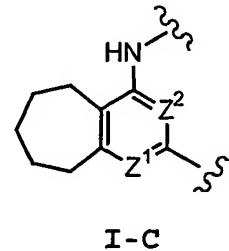
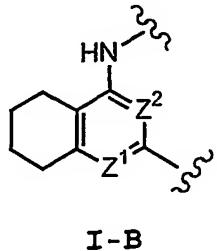
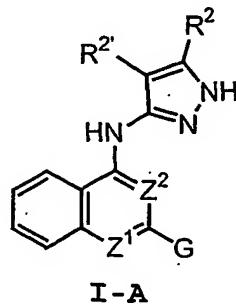
Compounds of this invention may exist in 5 alternative tautomeric forms, as in tautomers 1 and 2 shown below. Unless otherwise indicated, the representation of either tautomer is meant to include the other.

10

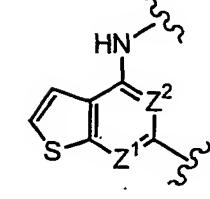
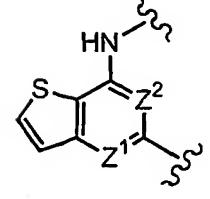
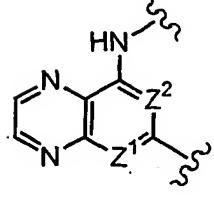
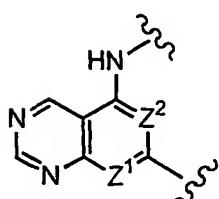
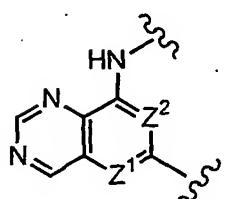
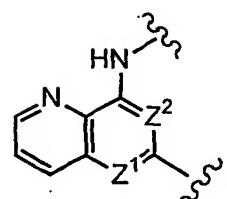
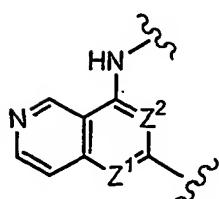
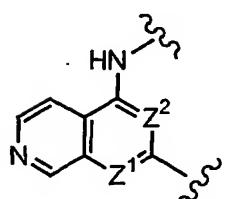
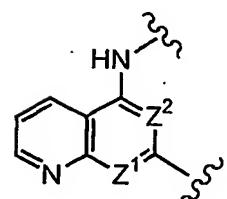
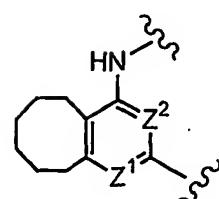
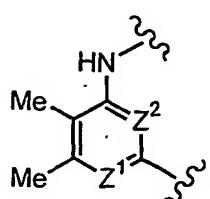
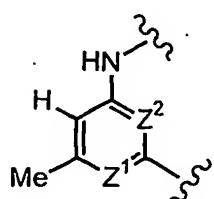
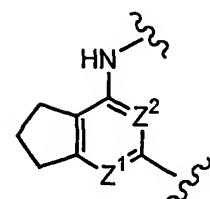
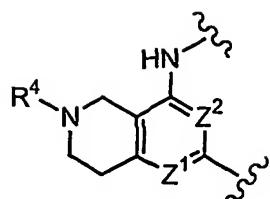
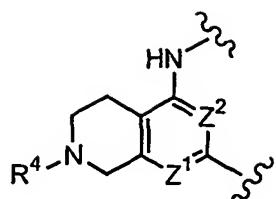


20

R^x and R^y (at positions Z^3 and Z^4 , respectively) may be taken together to form a fused ring, providing a 15 bicyclic ring system containing Ring A. Preferred R^x/R^y rings include a 5-, 6-, 7-, or 8-membered unsaturated or partially unsaturated ring having 0-2 heteroatoms, wherein said R^x/R^y ring is optionally substituted. Examples of Ring A systems are shown below by compounds 20 I-A through I-DD, wherein Z^1 is nitrogen or C(R^9) and Z^2 is nitrogen or C(H).

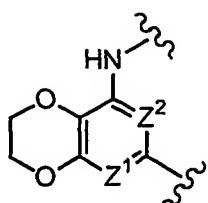


25

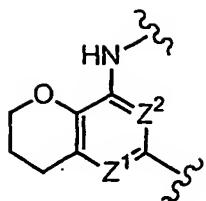


10

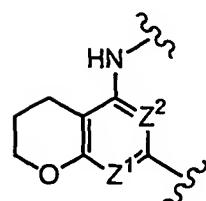
15



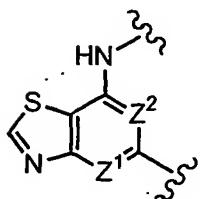
I-S



I-T

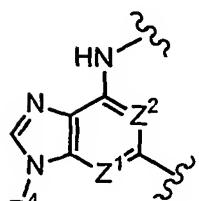


I-U

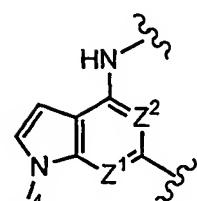


5

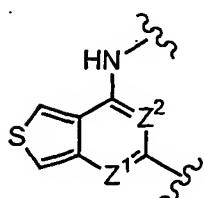
I-V



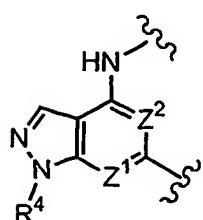
I-W



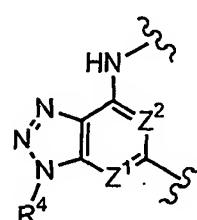
I-X



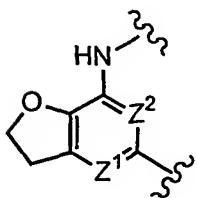
I-Y



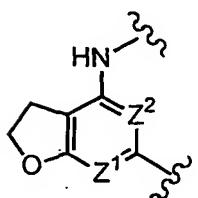
I-Z



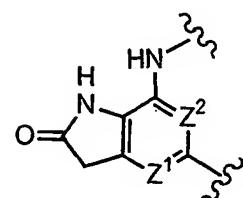
I-AA



I-BB



I-CC



I-DD

10

Preferred bicyclic Ring A systems include I-A, I-B, I-C, I-D, I-E, I-F, I-G, I-H, I-I, I-J, I-K, I-L, and I-M, more preferably I-A, I-B, I-C, I-F, and I-H, and most preferably I-A, I-B, and I-H.

15

In the monocyclic Ring A system, preferred R^x groups, when present, include hydrogen, alkyl- or dialkylamino, acetamido, or a C₁₋₄ aliphatic group such as methyl, ethyl, cyclopropyl, isopropyl or t-butyl.

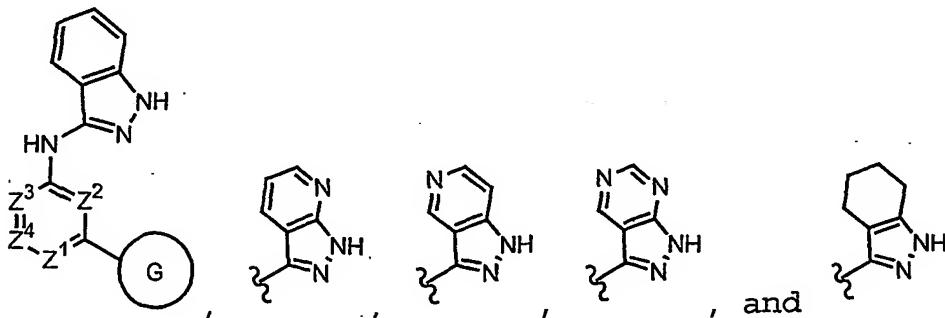
20

Preferred R^y groups, when present, include T-R³ wherein T is a valence bond or a methylene, and R³ is -R, -N(R⁴)₂,

or -OR. Examples of preferred R^y include 2-pyridyl, 4-pyridyl, piperidinyl, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or dialkylamino, acetamido, optionally substituted phenyl such as phenyl or halo-
5 substituted phenyl, and methoxymethyl.

In the bicyclic Ring A system, the ring formed when R^x and R^y are taken together may be substituted or unsubstituted. Suitable substituents include -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R,
10 -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR,
-N(R⁴)CO₂ (optionally substituted C₁₋₆ aliphatic),
-N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂,
-N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, wherein R and
15 R⁴ are as defined above. Preferred R^x/R^y ring substituents include -halo, -R, -OR, -COR, -CO₂R,
-CON(R⁴)₂, -CN; or -N(R⁴)₂ wherein R is hydrogen or an
optionally substituted C₁₋₆ aliphatic group.

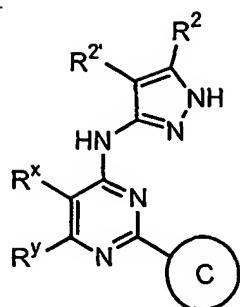
R² and R^{2'} may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring, wherein said fused ring is optionally substituted. These are exemplified in the following formula I compounds having a pyrazole-containing bicyclic
25 ring system:



Preferred substituents on the R²/R^{2'} fused ring include one or more of the following: -halo, -N(R⁴)₂, -C₁₋₃ alkyl, -C₁₋₃ haloalkyl, -NO₂, -O(C₁₋₃ alkyl), -CO₂(C₁₋₃ alkyl), -CN, -SO₂(C₁₋₃ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₃ alkyl), -NHC(O)(C₁₋₃ alkyl), -C(O)NH₂, and -CO(C₁₋₃ alkyl), wherein the (C₁₋₃ alkyl) is most preferably methyl.

When the pyrazole ring system is monocyclic, preferred R² groups include hydrogen, C₁₋₄ aliphatic, alkoxycarbonyl, (un)substituted phenyl, hydroxyalkyl, alkoxyalkyl, aminocarbonyl, mono- or dialkylaminocarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonyl, and (N-heterocyclyl)carbonyl. Examples of such preferred R² substituents include methyl, cyclopropyl, ethyl, isopropyl, propyl, t-butyl, cyclopentyl, phenyl, CO₂H, CO₂CH₃, CH₂OH, CH₂OCH₃, CH₂CH₂CH₂OH, CH₂CH₂CH₂OCH₃, CH₂CH₂CH₂OCH₂Ph, CH₂CH₂CH₂NH₂, CH₂CH₂CH₂NHCOOC(CH₃)₃, CONHCH(CH₃)₂, CONHCH₂CH=CH₂, CONHCH₂CH₂OCH₃, CONHCH₂Ph, CONH(cyclohexyl), CON(Et)₂, CON(CH₃)CH₂Ph, CONH(n-C₃H₇), CON(Et)CH₂CH₂CH₃, CONHCH₂CH(CH₃)₂, CON(n-C₃H₇)₂, CO(3-methoxymethylpyrrolidin-1-yl), CONH(3-tolyl), CONH(4-tolyl), CONHCH₃, CO(morpholin-1-yl), CO(4-methylpiperazin-1-yl), CONHCH₂CH₂OH, CONH₂, and CO(piperidin-1-yl). A preferred R^{2'} group is hydrogen.

An embodiment that is particularly useful for treating GSK3-mediated diseases relates to compounds of formula II:



II

or a pharmaceutically acceptable derivative or prodrug thereof, wherein;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring,

5 wherein said Ring C has one or two ortho substituents independently selected from -R¹, any substitutable non-ortho carbon position on Ring C is independently substituted by -R⁵, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or -R⁸;

15 R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo,

20 oxo, or -R⁸, said C₁₋₆ aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R¹ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

R^x and R^y are independently selected from T-R³, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8

membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or T-R³, and any substitutable nitrogen on said ring formed by R^x and R^y is substituted by R⁴;

T is a valence bond or a C₁₋₄ alkylidene chain;

R² and R^{2'} are independently selected from -R, -T-W-R⁶, or R² and R^{2'} are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms

5. selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R² and R^{2'} is substituted by halo, oxo, -CN, -NO₂, -R⁷, or -V-R⁶, and any substitutable nitrogen on said ring formed by R² and R^{2'} is substituted by R⁴;

R³ is selected from -R, -halo, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)CO₂ (optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁷)₂;

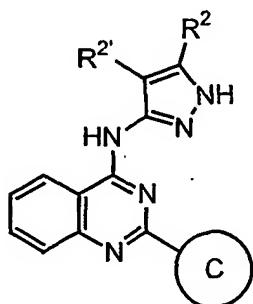
each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

10. each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂ (optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R⁵ is independently selected from -R, halo, -OR,
 -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR,
 -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR,
 -N(R⁴)CO₂ (optionally substituted C₁₋₆ aliphatic),
 5 -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂,
 -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, or R⁵ and
 an adjacent substituent taken together with their
 intervening atoms form said ring fused to Ring C;
 V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-,
 10 -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-,
 -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-,
 -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-,
 -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-,
 -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-,
 15 -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or
 -C(R⁶)₂N(R⁶)CON(R⁶)-;
 W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-,
 -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-,
 -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-,
 20 -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-,
 -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-,
 -C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;
 each R⁶ is independently selected from hydrogen, an
 optionally substituted C₁₋₄ aliphatic group, or two R⁶
 25 groups on the same nitrogen atom are taken together
 with the nitrogen atom to form a 5-6 membered
 heterocyclyl or heteroaryl ring;
 each R⁷ is independently selected from hydrogen or an
 optionally substituted C₁₋₆ aliphatic group, or two R⁷
 30 on the same nitrogen are taken together with the
 nitrogen to form a 5-8 membered heterocyclyl or
 heteroaryl ring; and

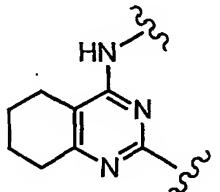
each R⁸ is independently selected from an optionally substituted C₁₋₄ aliphatic group, -OR⁶, -SR⁶, -COR⁶, -SO₂R⁶, -N(R⁶)₂, -N(R⁶)N(R⁶)₂, -CN, -NO₂, -CON(R⁶)₂, or -CO₂R⁶.

5 When the R^x and R^y groups of formula II are taken together to form a fused ring, preferred R^x/R^y rings include a 5-, 6-, 7-, or 8-membered unsaturated or partially unsaturated ring having 0-2 heteroatoms, wherein said R^x/R^y ring is optionally substituted. This
10 provides a bicyclic ring system containing a pyrimidine ring. Examples of preferred pyrimidine ring systems of formula II are the mono- and bicyclic systems shown below.

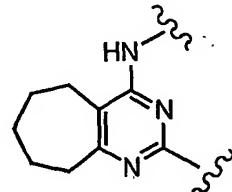


15

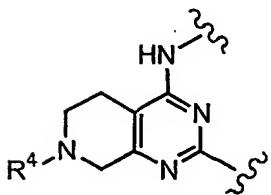
III-A



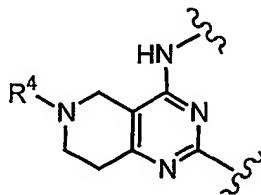
III-B



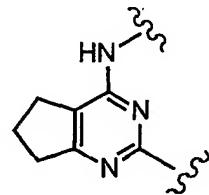
III-C



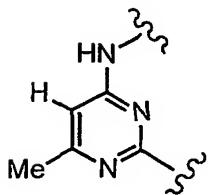
III-D



III-E

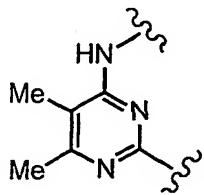


III-F

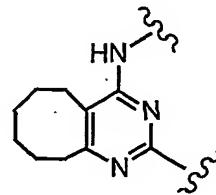


20

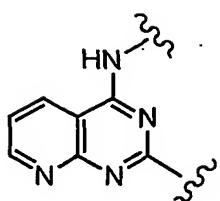
III-G



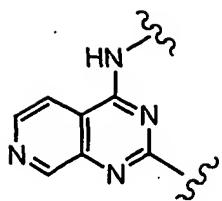
III-H



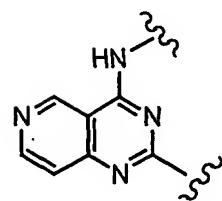
III-I



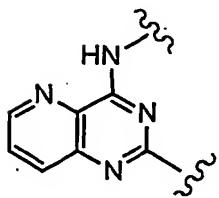
II-J



II-K

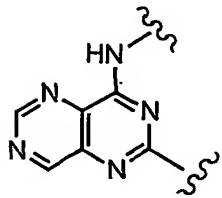


II-L

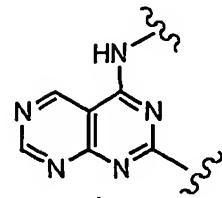


5

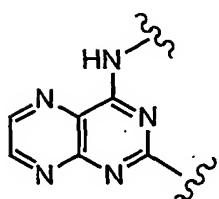
II-M



II-N



II-O



II-P

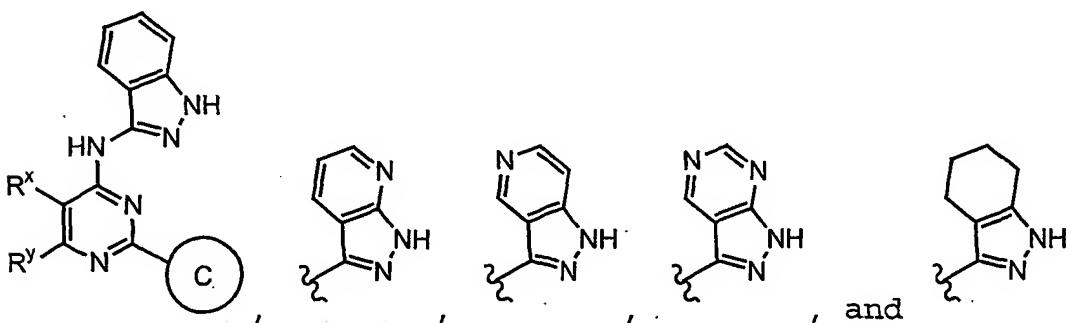
10 More preferred pyrimidine ring systems of formula II include II-A, II-B, II-C, II-F, and II-H, most preferably II-A, II-B, and II-H.

In the monocyclic pyrimidine ring system of formula II, preferred R^x groups include hydrogen, alkyl- or dialkylamino, acetamido, or a C₁₋₄ aliphatic group such as methyl, ethyl, cyclopropyl, isopropyl or t-butyl. Preferred R^y groups include T-R³ wherein T is a valence bond or a methylene, and R³ is -R, -N(R⁴)₂, or -OR. When R³ is -R or -OR, a preferred R is an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring. Examples of preferred R^y include 2-pyridyl, 4-pyridyl, piperidinyl, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or dialkylamino, acetamido, optionally substituted phenyl

such as phenyl or halo-substituted phenyl, and methoxymethyl.

In the bicyclic pyrimidine ring system of formula II, the ring formed when R^x and R^y are taken together may be substituted or unsubstituted. Suitable substituents include -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, wherein R and R⁴ are as defined above. Preferred R^x/R^y ring substituents include -halo, -R, -OR, -COR, -CO₂R, -CON(R⁴)₂, -CN, or -N(R⁴)₂ wherein R is an optionally substituted C₁₋₆ aliphatic group.

The R² and R^{2'} groups of formula II may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring. These are exemplified in the following formula II compounds having a pyrazole-containing bicyclic ring system:



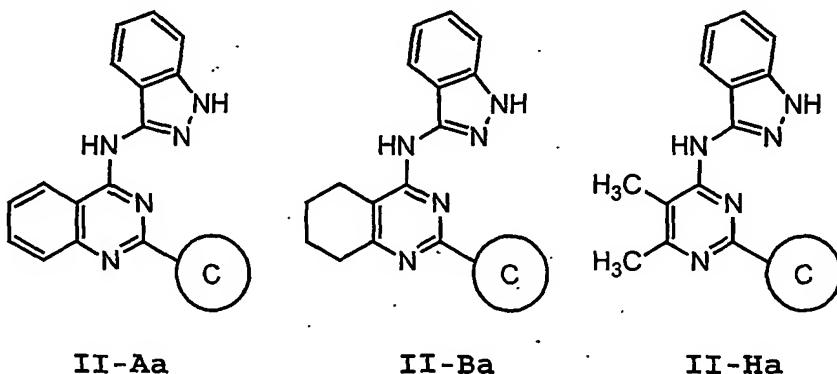
Preferred substituents on the R²/R^{2'} fused ring of formula II include one or more of the following: -halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, -SO₂(C₁₋₄ alkyl), -SO₂NH₂,

-OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂; and -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C₁₋₄ alkyl) group is methyl.

5 When the pyrazole ring system of formula II is monocyclic, preferred R² groups include hydrogen, a substituted or unsubstituted group selected from aryl, heteroaryl, or a C₁₋₆ aliphatic group. Examples of such preferred R² groups include methyl, t-butyl, -CH₂OCH₃, 10 cyclopropyl, furanyl, thienyl, and phenyl. A preferred R²' group is hydrogen.

More preferred ring systems of formula II are the following, which may be substituted as described above, wherein R² and R²' are taken together with the 15 pyrazole ring to form an indazole ring; and R^x and R^y are each methyl; or R^x and R^y are taken together with the pyrimidine ring to form a quinazoline or tetrahydroquinazoline ring:

20



II-Aa

II-Ba

II-Ha

Particularly preferred are those compounds of formula II-Aa, II-Ba, or II-Ha wherein ring C is a phenyl ring and R¹ is halo, methyl, or trifluoromethyl.

Preferred formula II Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is

contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring. Such rings preferably are fused at ortho and meta positions of Ring C. Examples of preferred bicyclic Ring C systems include 5 naphthyl, quinolinyl and isoquinolinyl.

An important feature of the formula II compounds is the R¹ ortho substituent on Ring C. An ortho position on Ring C or Ring D is defined relative to the position where Ring A is attached. Preferred R¹ groups 10 include -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶. When R¹ is an optionally substituted C₁₋₆ aliphatic group, the most preferred optional substituents are halogen. Examples of 15 preferred R¹ groups include -CF₃, -Cl, -F, -CN, -COCH₃, -OCH₃, -OH, -CH₂CH₃, -OCH₂CH₃, -CH₃, -CF₂CH₃, cyclohexyl, t-butyl, isopropyl, cyclopropyl, -C≡CH, -C≡C-CH₃, -SO₂CH₃, -SO₂NH₂, -N(CH₃)₂, -CO₂CH₃, -CONH₂, -NHCOCH₃, -OC(O)NH₂, -NHSO₂CH₃, and -OCF₃.

20 On Ring C of formula II, preferred R⁵ substituents, when present, include -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, and -N(R⁴)SO₂R. More preferred R⁵ substituents include -Cl, 25 -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic). Examples of such preferred R⁵ substituents include -Cl, -F, -CN, -CF₃, -NH₂, -NHMe, -NMe₂, -OEt, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and -CO₂Et.

30 Preferred formula II compounds have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring;

(b) R^x is hydrogen or C₁₋₄ aliphatic and R^y is T-R³, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted 5-7 membered unsaturated or partially unsaturated ring having 0-2 ring nitrogens;

(c) R¹ is -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶; and

(d) R²' is hydrogen and R² is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C₁₋₆ aliphatic group, or R² and R²' are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula II have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;

(b) R^x is hydrogen or methyl and R^y is -R, N(R⁴)₂, or -OR, or R^x and R^y are taken together with their intervening atoms to form a 5-7 membered unsaturated or partially unsaturated carbocyclo ring optionally substituted with -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂,

$\text{-SO}_2\text{N}(\text{R}^4)_2$, -OC(=O)R , $\text{-N}(\text{R}^4)\text{COR}$, $\text{-N}(\text{R}^4)\text{CO}_2$ (optionally substituted C_{1-6} aliphatic), $\text{-N}(\text{R}^4)\text{N}(\text{R}^4)_2$, $\text{-C=NN}(\text{R}^4)_2$, -C=N-OR , $\text{-N}(\text{R}^4)\text{CON}(\text{R}^4)_2$, $\text{-N}(\text{R}^4)\text{SO}_2\text{N}(\text{R}^4)_2$, $\text{-N}(\text{R}^4)\text{SO}_2\text{R}$, or $\text{-OC(=O)N}(\text{R}^4)_2$;

5 (c) R^1 is -halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, or $-\text{CN}$;

(d) R^2' is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, or a C_{1-6} aliphatic group, or R^2 and R^2' are taken together 10 with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring; and

(e) each R^5 is independently selected from -halo, $-\text{CN}$, $-\text{NO}_2$, $\text{-N}(\text{R}^4)_2$, optionally substituted C_{1-6} 15 aliphatic group, $-\text{OR}$, $-\text{C(O)R}$, $-\text{CO}_2\text{R}$, $-\text{CONH}(\text{R}^4)$, $-\text{N}(\text{R}^4)\text{COR}$, $-\text{SO}_2\text{N}(\text{R}^4)_2$, or $-\text{N}(\text{R}^4)\text{SO}_2\text{R}$.

Even more preferred compounds of formula II have one or more, and more preferably all, of the features selected from the group consisting of:

20 (a) Ring C is a phenyl ring optionally substituted by $-\text{R}^5$;

(b) R^x is hydrogen or methyl and R^y is methyl, methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or an optionally substituted group selected from 25 2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted benzo ring or partially unsaturated 6-membered carbocyclo ring;

(c) R^1 is -halo, a C_{1-4} aliphatic group 30 optionally substituted with halogen, or $-\text{CN}$;

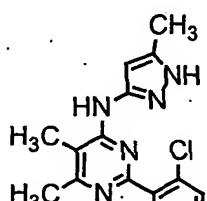
(d) R^2 and R^2' are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring

optionally substituted with -halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, or -CO(C₁₋₄ alkyl), wherein
5 the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group; and

(e) each R⁵ is independently selected from -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and
10 -CO₂(C₁₋₄ aliphatic).

Representative compounds of formula II are shown below in Table 1.

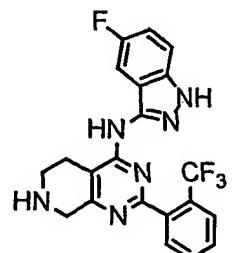
Table 1.



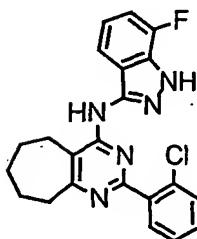
II-1



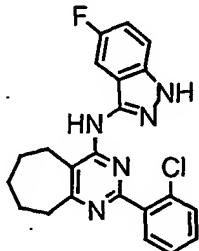
II-2



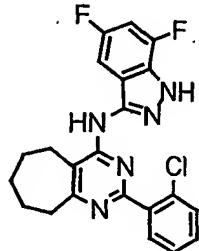
II-3



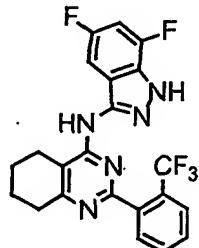
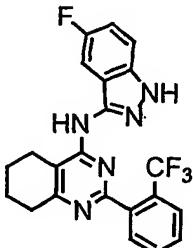
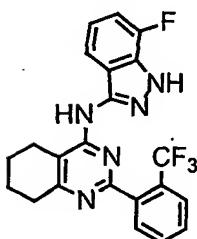
II-4



II-5

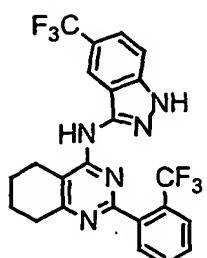


II-6

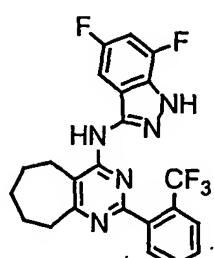


20

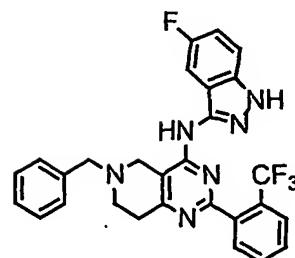
II-7



II-8



II-9

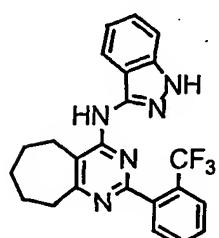


II-10

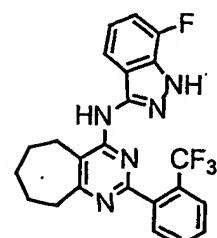
II-11

II-12

5



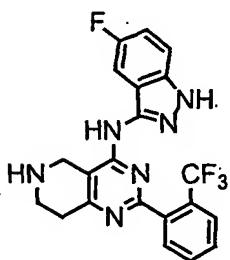
II-13



II-14



II-15

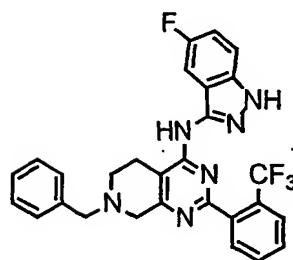


10

II-16



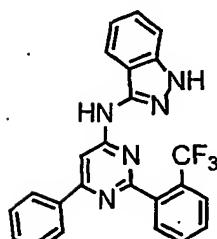
II-17



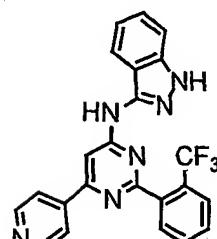
II-18



II-19

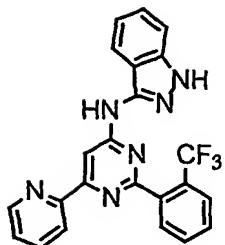


II-20

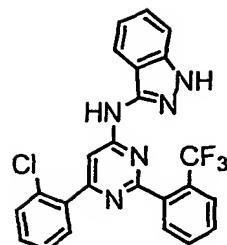


II-21

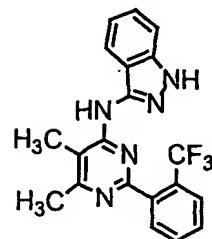
15



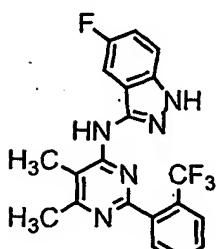
II-22



II-23

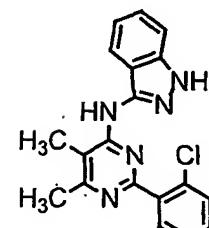


II-24

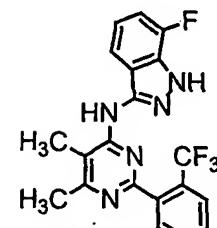


5

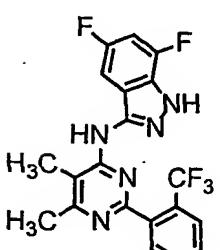
II-25



II-26



II-27



II-28



II-29

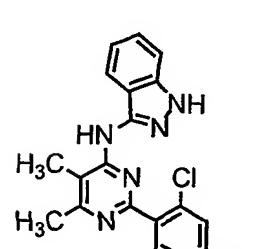


II-30

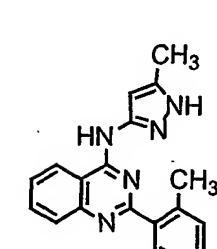


10

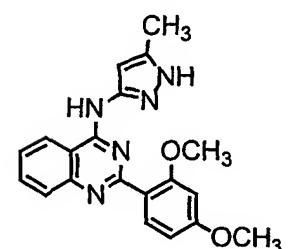
II-31



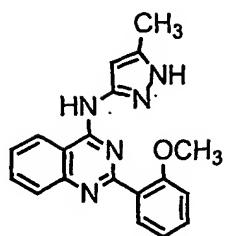
II-32



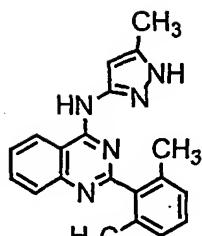
II-33



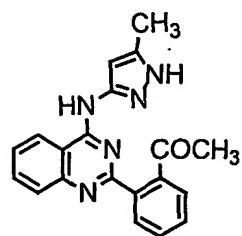
II-34



II-35



II-36

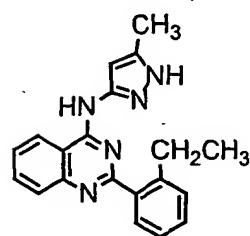
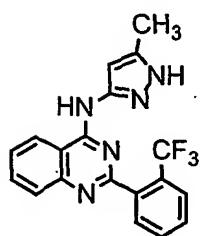
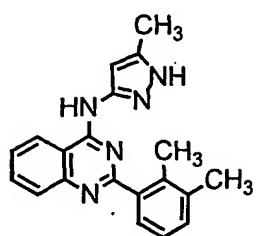


II-37

II-38

II-39

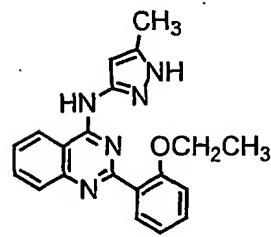
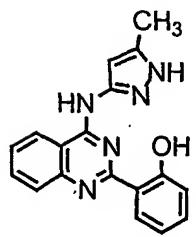
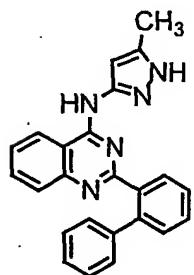
5



II-40

II-41

II-42

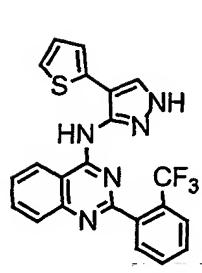
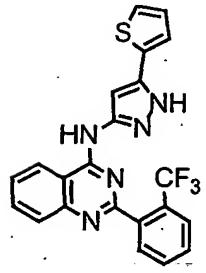


10

II-43

II-44

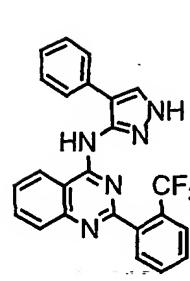
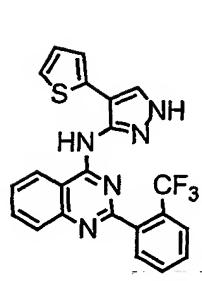
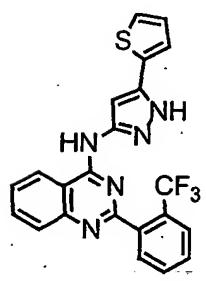
II-45

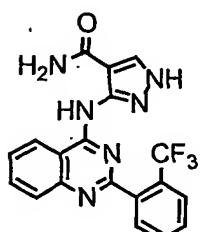
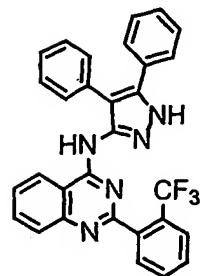
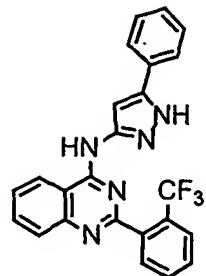
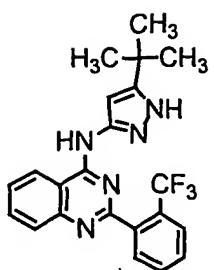


II-46

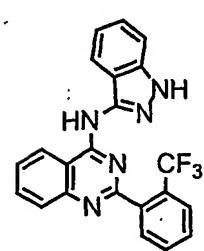
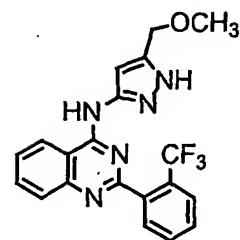
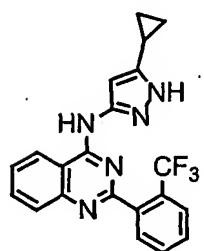
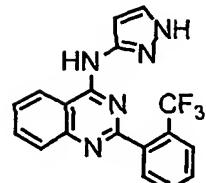
II-47

II-48

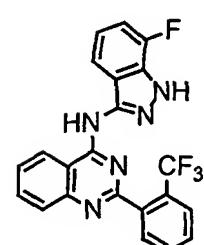
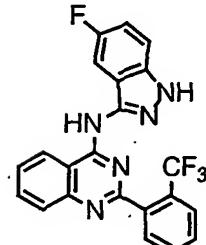


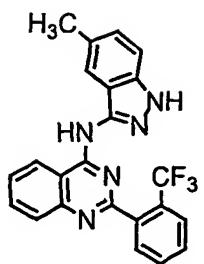


II-52



II-58





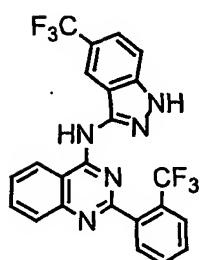
II-61



II-62

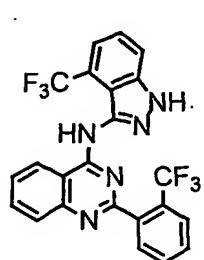


II-63

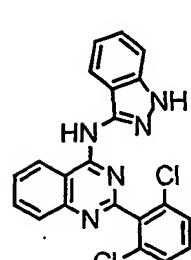


5

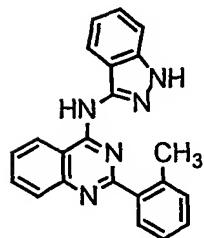
II-64



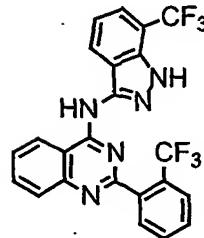
II-65



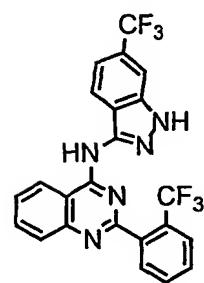
II-66



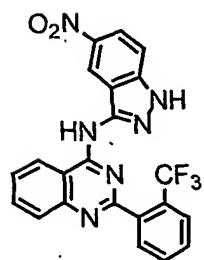
II-67



II-68

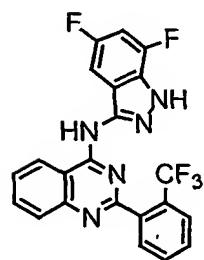


II-69

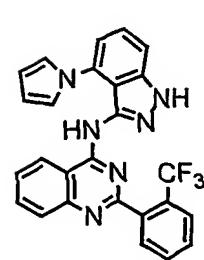


10

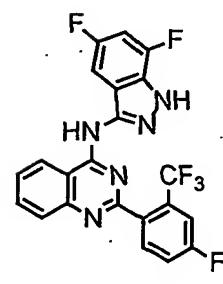
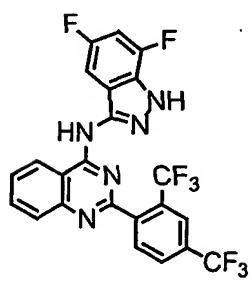
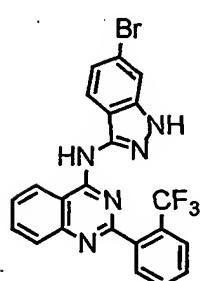
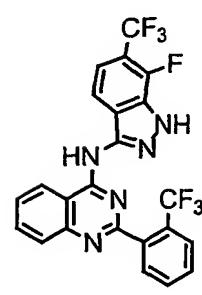
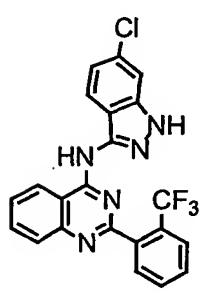
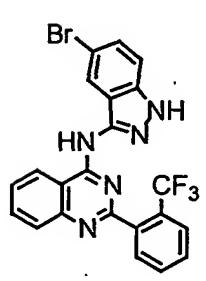
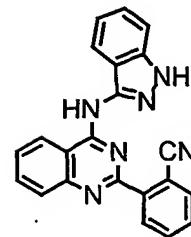
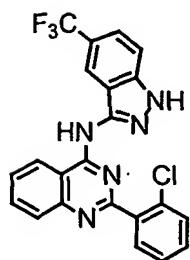
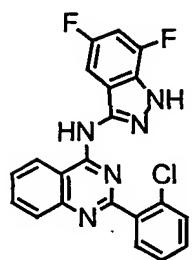
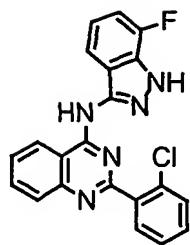
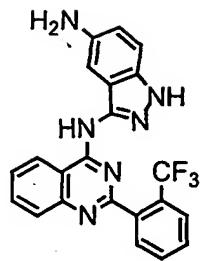
II-70

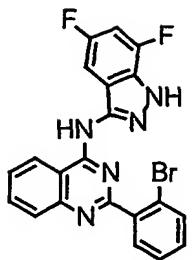


II-71

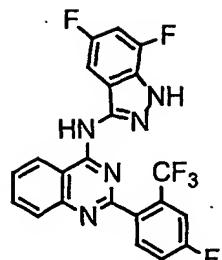


II-72





II-85



II-86



II-87

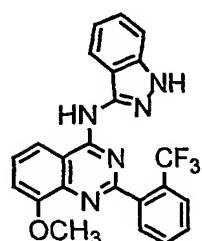


5

II-88



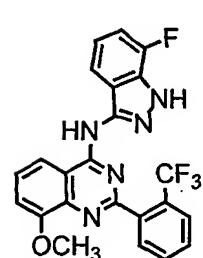
II-89



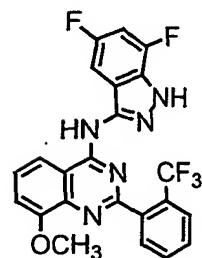
II-90



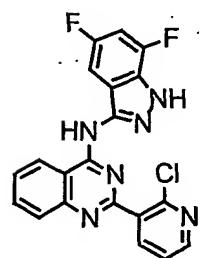
II-91



II-92



II-93

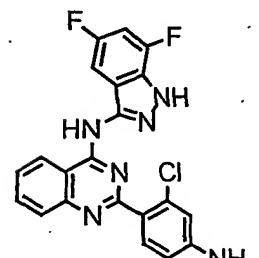


10

II-94



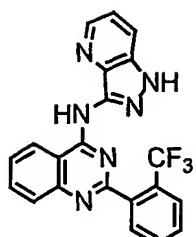
II-95



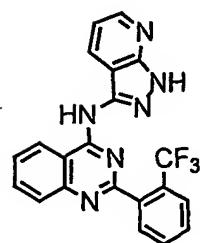
II-96



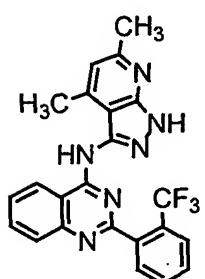
II-97



II-98

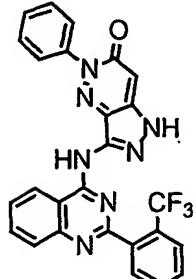


II-99

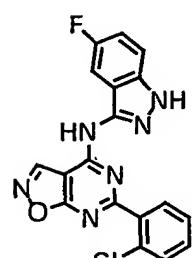


5

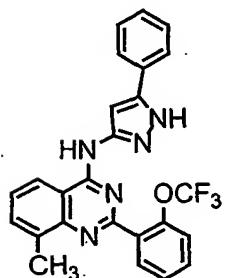
II-100



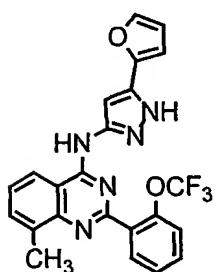
II-101



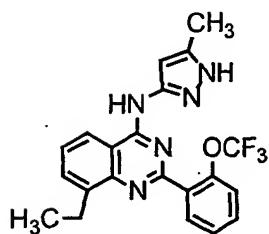
II-102



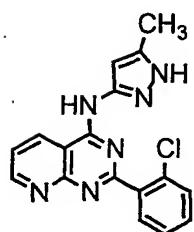
II-103



II-104

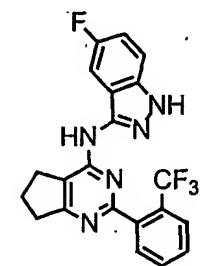


II-105

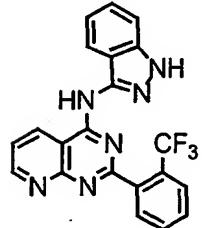


10

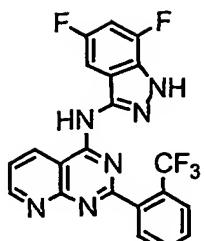
II-106



II-107



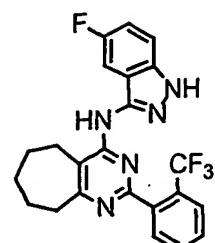
II-108



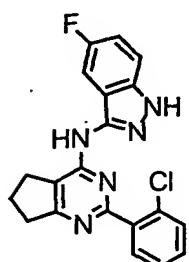
II-109



II-110



II-111

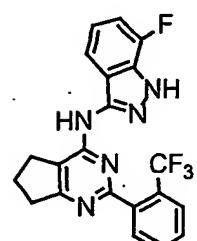


5

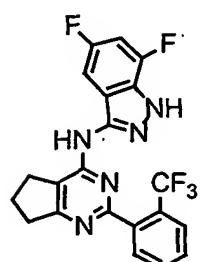
II-112



II-113



II-114



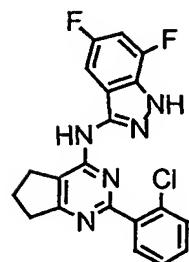
II-115



II-116

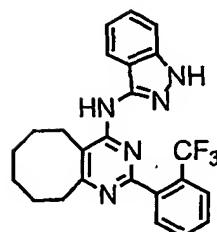


II-117

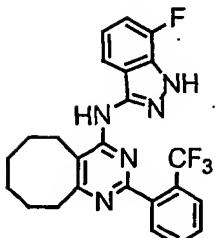


10

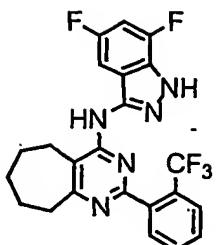
II-118



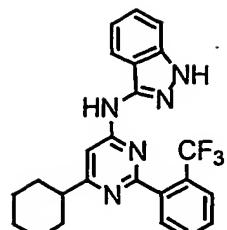
II-119



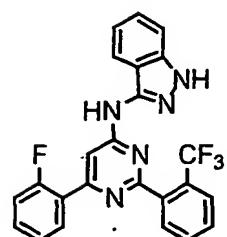
II-120



II-121



II-122

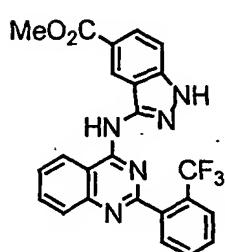


II-123

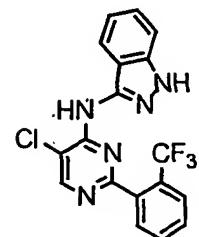


5

II-124



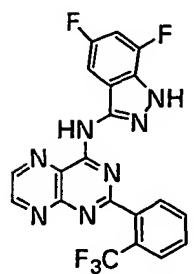
II-125



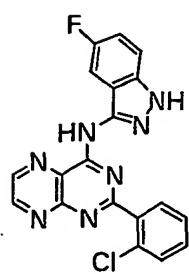
II-126



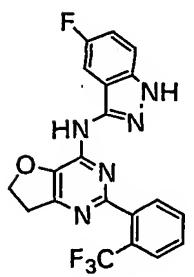
II-127



II-128

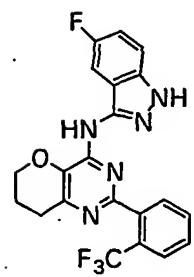


II-129



10

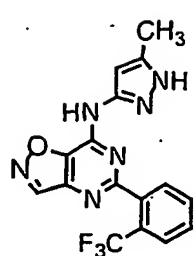
II-130



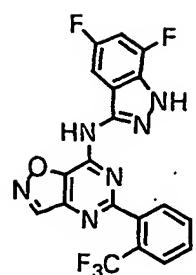
II-131



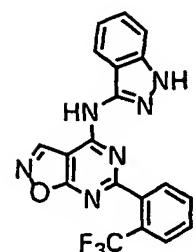
II-132



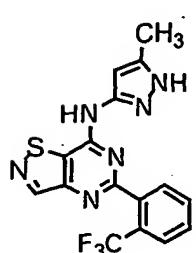
II-133



II-134

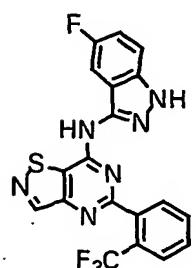


II-135

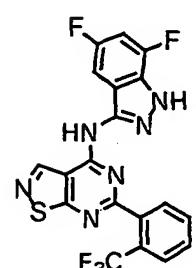


5

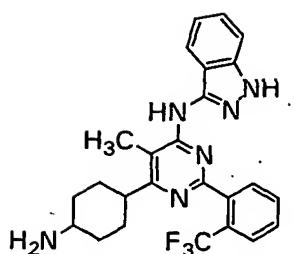
II-136



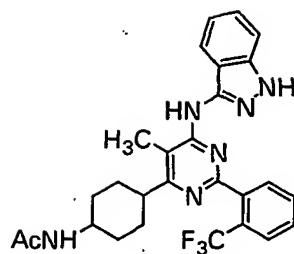
II-137



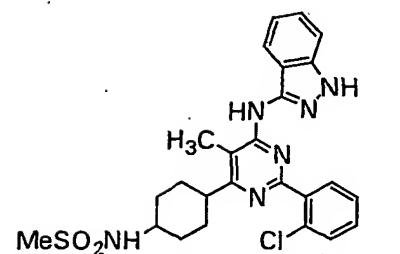
II-138



II-139



II-140

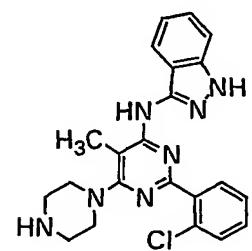


II-141

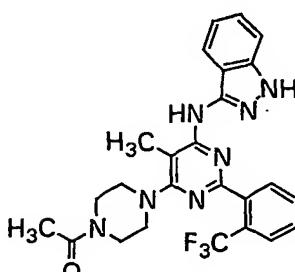
10



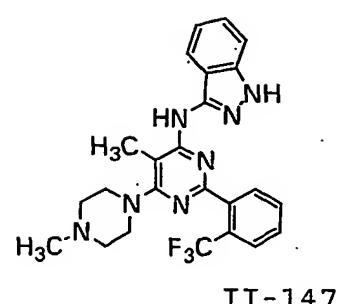
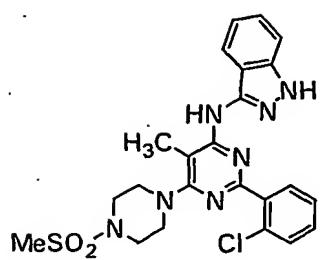
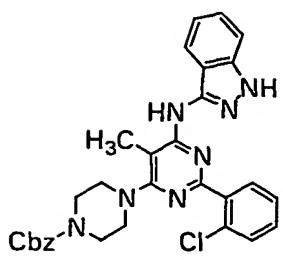
II-142



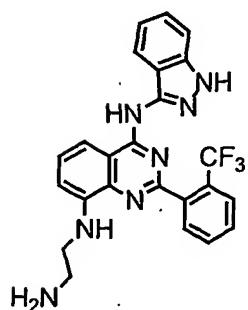
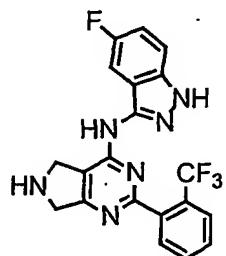
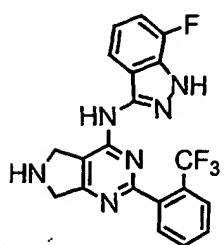
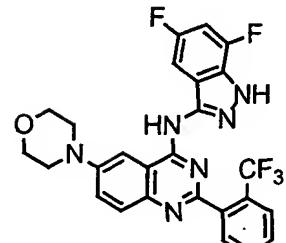
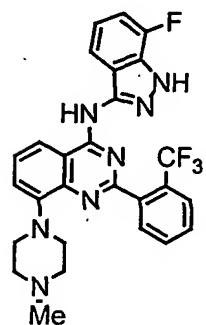
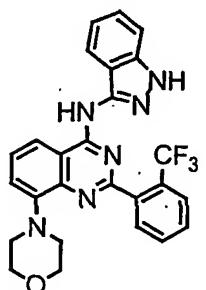
II-143



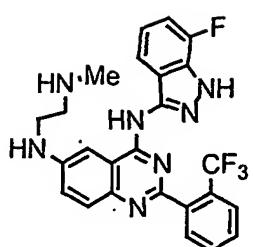
II-144



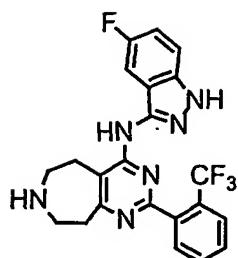
5



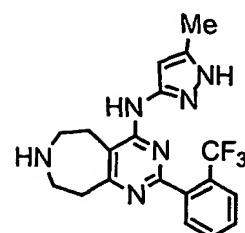
10



II-154



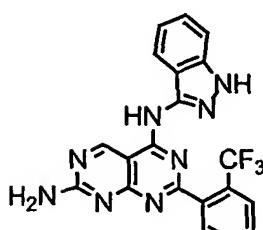
II-155



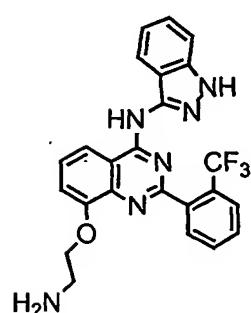
II-156



II-157

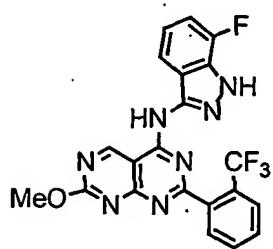


II-158

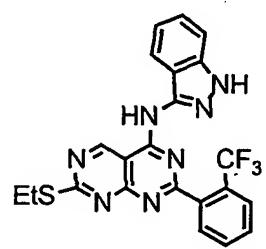


II-159

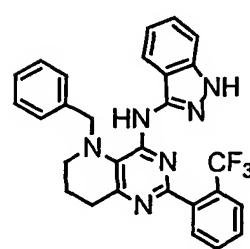
5



II-160

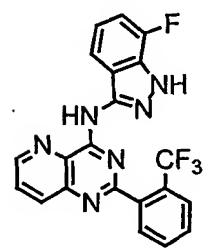


II-161



II-162

10



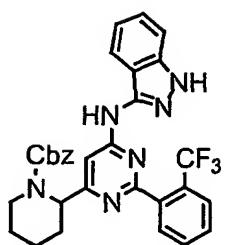
II-163



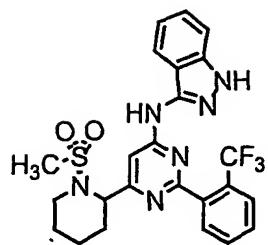
II-164



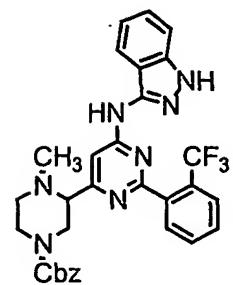
II-165



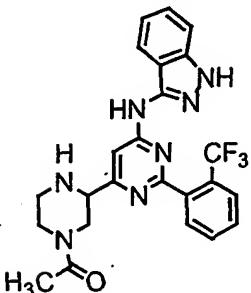
II-166



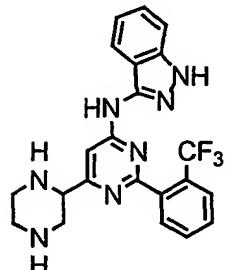
II-167



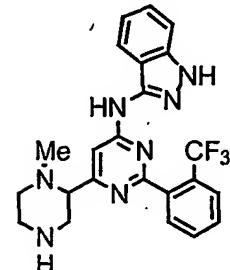
II-168



II-169

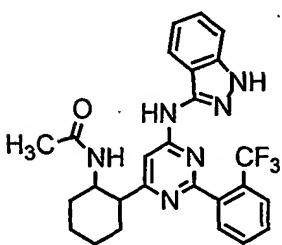


II-170

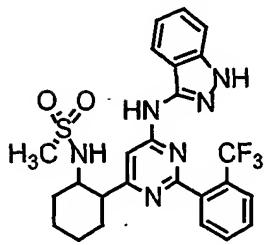


II-171

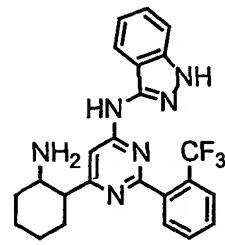
5



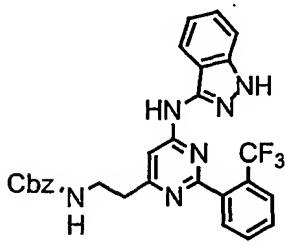
II-172



II-173

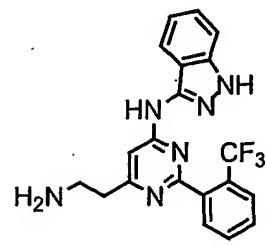


II-174

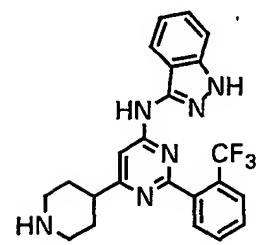


10

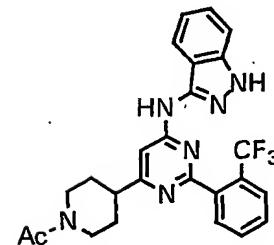
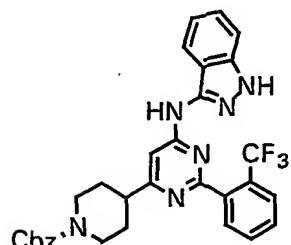
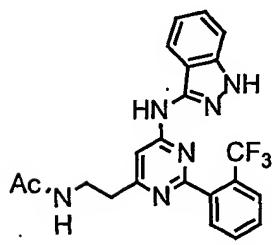
II-175



II-176



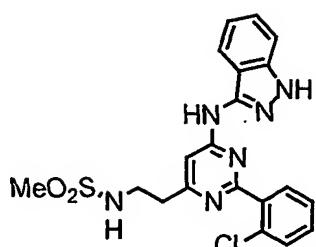
II-177



II-178

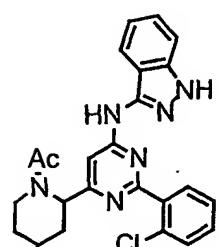
II-179

II-180

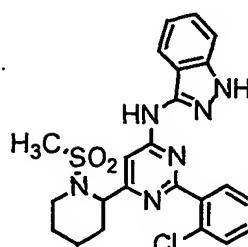


5

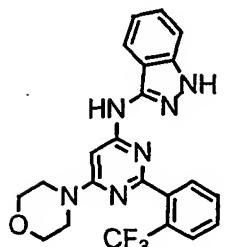
II-181



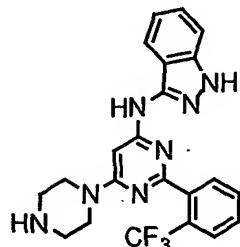
II-182



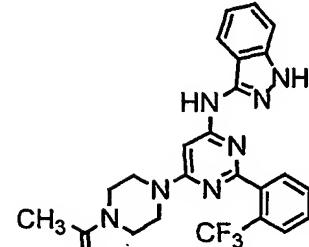
II-183



II-184

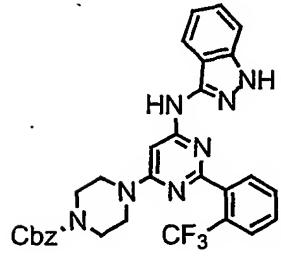


II-185

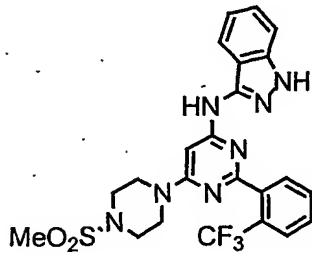


II-186

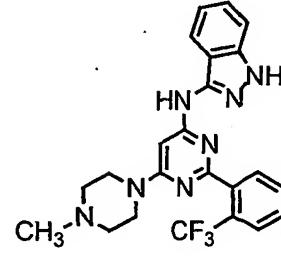
10



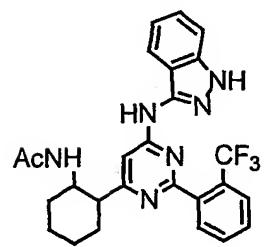
II-187



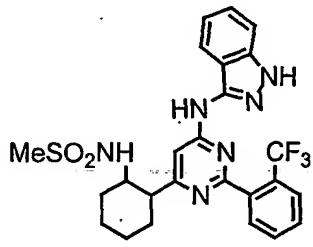
II-188



II-189



II-190

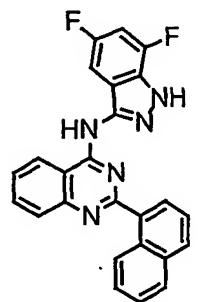
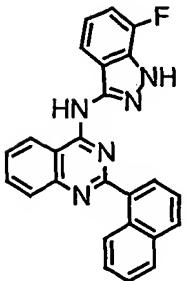
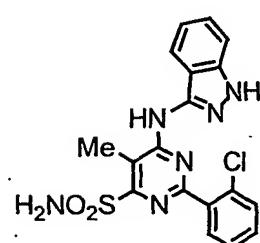
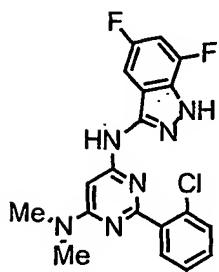
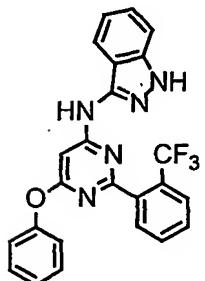
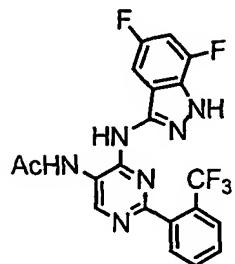
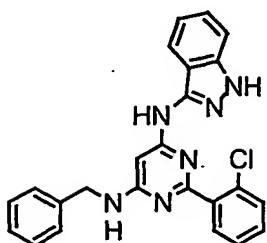
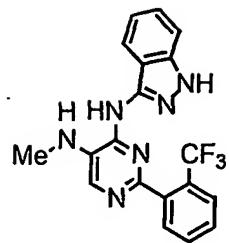
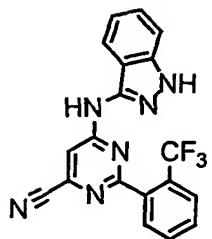


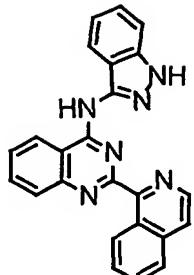
II-191



II-192

15





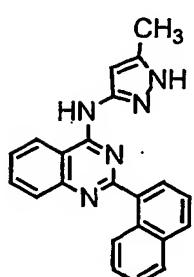
II-205



II-206

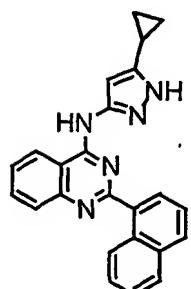


II-207



5

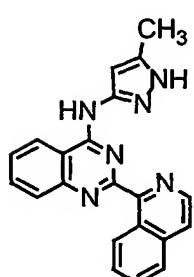
II-208



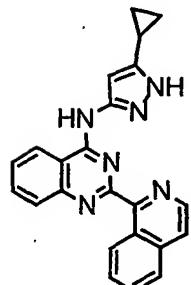
II-209



II-210



II-211



II-212

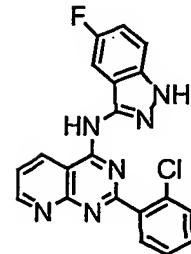


II-213

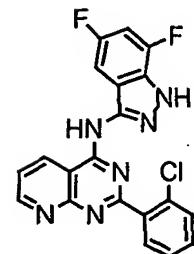


10

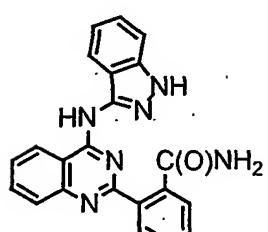
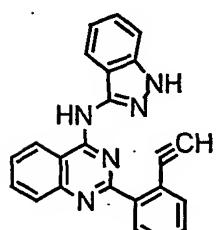
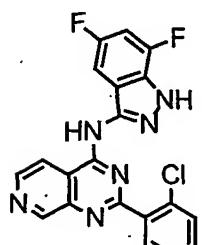
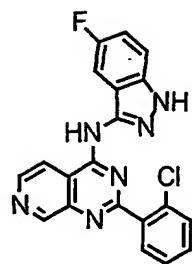
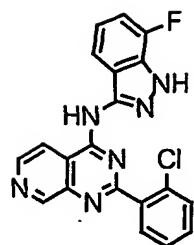
II-214



II-215

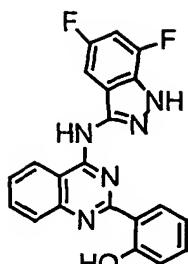


II-216





II-229



II-230

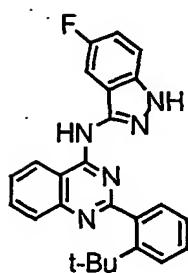


II-231



5

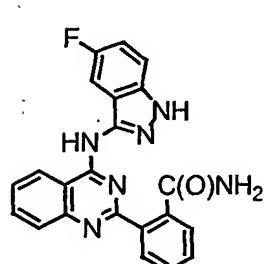
II-232



II-233



II-234



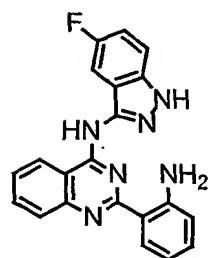
II-235



II-236



II-237



10

II-238



II-239



II-240



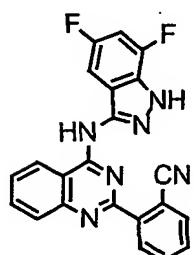
II-241



II-242

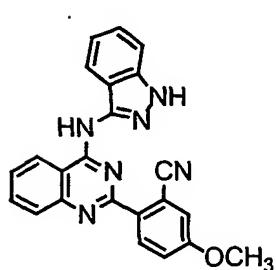


II-243

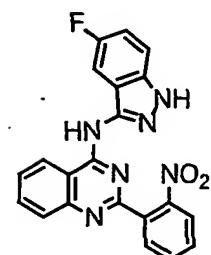


5

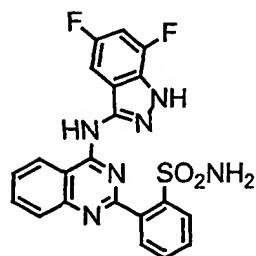
II-244



II-245



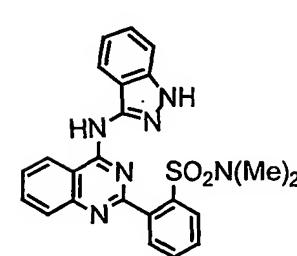
II-246



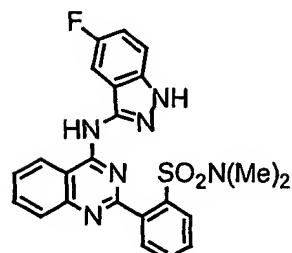
II-247



II-248



II-249



10

II-250



II-251

10

In another embodiment, this invention provides
a composition comprising a compound of formula II and a
15 pharmaceutically acceptable carrier.

One aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound 5 of formula II.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a GSK-3 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a 10 therapeutically effective amount of a composition comprising a compound of formula II.

Another aspect relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising 15 administering to said patient a therapeutically effective amount of a composition comprising a compound of formula II. This method is especially useful for diabetic patients.

Another aspect relates to a method of 20 inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula II. This method is especially useful in halting or 25 slowing the progression of Alzheimer's disease.

Another aspect relates to a method of inhibiting the phosphorylation of β -catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition 30 comprising a compound of formula II. This method is especially useful for treating schizophrenia.

One aspect of this invention relates to a method of inhibiting Aurora activity in a patient,

comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula II.

Another aspect relates to a method of treating
5 a disease that is alleviated by treatment with an Aurora inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula II. This method is
10 especially useful for treating cancer, such as colon, ovarian, and breast cancer.

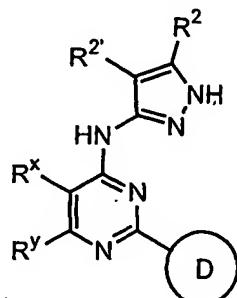
One aspect of this invention relates to a method of inhibiting CDK-2 activity in a patient, comprising administering to the patient a therapeutically
15 effective amount of a composition comprising a compound of formula II.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a CDK-2 inhibitor, said method comprising the step of
20 administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula II. This method is especially useful for treating cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis,
25 cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid arthritis.

Another method relates to inhibiting GSK-3, Aurora, or CDK-2 activity in a biological sample, which
30 method comprises contacting the biological sample with the GSK-3 or Aurora inhibitor of formula II, or a pharmaceutical composition thereof, in an amount effective to inhibit GSK-3, Aurora or CDK-2.

Each of the aforementioned methods directed to the inhibition of GSK-3, Aurora or CDK-2, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula II, as 5 described above.

Another embodiment of this invention relates to compounds of formula III:



III

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

- 10 Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or -R⁵, and at any substitutable ring nitrogen by -R⁴, provided that when Ring D is a six-membered aryl or heteroaryl ring, -R⁵ is hydrogen at each ortho carbon position of Ring D;
- 15 R^x and R^y are taken together with their intervening atoms to form a fused, benzo ring or a 5-8 membered carbocyclo ring, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or T-R³;
- T is a valence bond or a C₁₋₄ alkylidene chain;

R² and R^{2'} are independently selected from -R, -T-W-R⁶, or R² and R^{2'} are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms

5 selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R² and R^{2'} is substituted by halo, oxo, -CN, -NO₂, -R⁷, or -V-R⁶, and any substitutable nitrogen on said ring formed by R² and R^{2'} is substituted by R⁴;

10 R³ is selected from -R, -halo, =O, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂,

15 -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

20 each R⁵ is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂,

25 -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-,

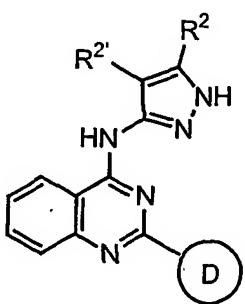
-N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-,
 -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-,
 -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-,
 -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-,
 5 -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or
 -C(R⁶)₂N(R⁶)CON(R⁶)-;
 W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-,
 -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-,
 -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-,
 10 -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-,
 -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-,
 -C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;
 each R⁶ is independently selected from hydrogen or an
 optionally substituted C₁₋₄ aliphatic group, or two R⁶
 15 groups on the same nitrogen atom are taken together
 with the nitrogen atom to form a 5-6 membered
 heterocyclyl or heteroaryl ring; and
 each R⁷ is independently selected from hydrogen or an
 optionally substituted C₁₋₆ aliphatic group, or two R⁷
 20 on the same nitrogen are taken together with the
 nitrogen to form a 5-8 membered heterocyclyl or
 heteroaryl ring.

Preferred formula III Ring D monocyclic rings
 include substituted and unsubstituted phenyl, pyridinyl,
 25 piperidinyl, piperazinyl, pyrrolidinyl, thienyl,
 azepanyl, and morpholinyl rings. When two adjacent
 substituents on Ring D are taken together to form a fused
 ring, the Ring D system is bicyclic. Preferred formula
 III Ring D bicyclic rings include 1,2,3,4-
 30 tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl,
 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl,
 isoquinolinyl, quinolinyl, and naphthyl. Examples of

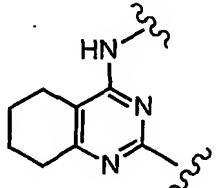
more preferred bicyclic Ring D systems include naphthyl and isoquinolinyl.

Preferred R⁵ substituents on Ring D of formula III include halo, oxo, CN, -NO₂, -N(R⁴)₂, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -SR, -OR, -C(O)R, or substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. More preferred R⁵ substituents include -halo, -CN, -oxo, -SR, -OR, -N(R⁴)₂, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. Examples of Ring D substituents include -OH, phenyl, methyl, CH₂OH, CH₂CH₂OH, pyrrolidinyl, OPh, CF₃, C≡CH, Cl, Br, F, I, NH₂, C(O)CH₃, i-propyl, tert-butyl, SEt, OMe, N(Me)₂, methylene dioxy, and ethylene dioxy.

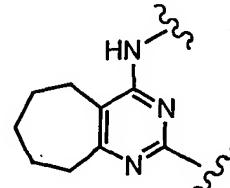
Preferred rings formed when the R^x and R^y groups of formula III are taken together to form a fused ring include a 5-, 6-, or 7-membered unsaturated or partially unsaturated carbocyclo ring, wherein any substitutable carbon on said fused ring is substituted by oxo or T-R³. Examples of preferred bicyclic ring systems are shown below.



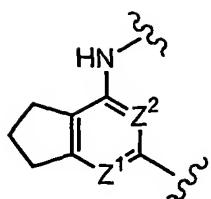
III-A



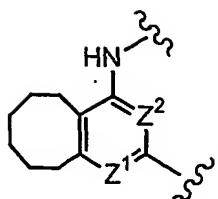
III-B



III-C



III-F



III-I

Preferred substituents on the R^x/R^y fused ring

5 of formula III include -R, oxo, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂ (optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or

10 -OC(=O)N(R⁴)₂, wherein R and R⁴ are as defined above.

More preferred substituents on the R^x/R^y fused ring include halo, CN, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, (C₁₋₆ alkyl)carbonyl, (C₁₋₆ alkyl)sulfonyl, mono- or dialkylamino, mono- or dialkylaminocarbonyl, mono- or

15 dialkylaminocarbonyloxy, or 5-6 membered heteroaryl.

Examples of such preferred substituents include methoxy, methyl, isopropyl, methylsulfonyl, cyano, chloro, pyrrolyl, methoxy, ethoxy, ethylamino, acetyl, and acetamido.

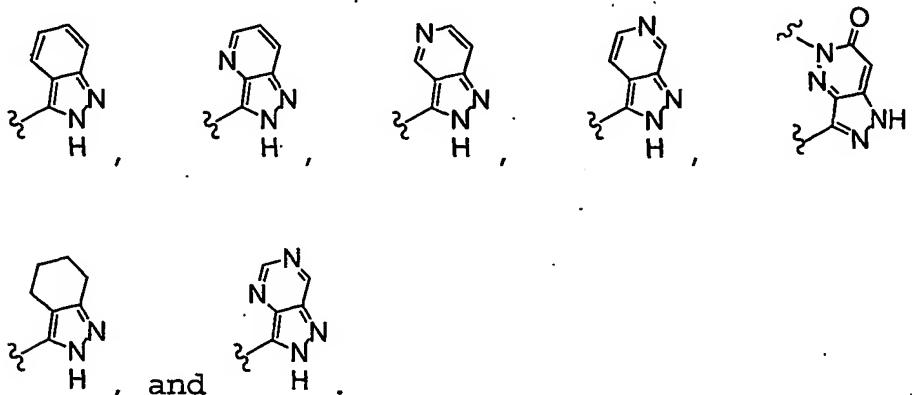
20 Preferred R² substituents of formula III include hydrogen, C₁₋₄ aliphatic, alkoxycarbonyl, (un)substituted phenyl, hydroxyalkyl, alkoxyalkyl, aminocarbonyl, mono- or dialkylaminocarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonyl, and (N-heterocyclyl)carbonyl. Examples of such preferred R²

25 substituents include methyl, cyclopropyl, ethyl, isopropyl, propyl, t-butyl, cyclopentyl, phenyl, CO₂H, CO₂CH₃, CH₂OH, CH₂OCH₃, CH₂CH₂CH₂OH, CH₂CH₂CH₂OCH₃, CH₂CH₂CH₂OCH₂Ph, CH₂CH₂CH₂NH₂, CH₂CH₂CH₂NHCOOC(CH₃)₃,

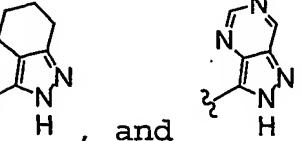
30 CONHCH(CH₃)₂, CONHCH₂CH=CH₂, CONHCH₂CH₂OCH₃, CONHCH₂Ph,

CONH(cyclohexyl), CON(Et)₂, CON(CH₃)CH₂Ph, CONH(n-C₃H₇), CON(Et)CH₂CH₂CH₃, CONHCH₂CH(CH₃)₂, CON(n-C₃H₇)₂, CO(3-methoxymethylpyrrolidin-1-yl), CONH(3-tolyl), CONH(4-tolyl), CONHCH₃, CO(morpholin-1-yl), CO(4-methylpiperazin-1-yl), CONHCH₂CH₂OH, CONH₂, and CO(piperidin-1-yl).

When the R² and R^{2'} groups of formula III are taken together to form a ring, preferred R²/R^{2'} ring systems containing the pyrazole ring include benzo, pyrido, pyrimido, 3-oxo-2H-pyridazino, and a partially unsaturated 6-membered carbocyclo ring. Examples of such preferred R²/R^{2'} ring systems containing the pyrazole ring include the following:



15



Preferred substituents on the R²/R^{2'} fused ring of formula III include one or more of the following:

-halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, and -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C₁₋₄ alkyl) group is methyl.

Preferred formula III compounds have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^x and R^y are taken together with their intervening atoms to form an optionally substituted benzo ring or a 5-7 membered carbocyclo ring; and

(c) R^{2'} is hydrogen or methyl and R² is T-W-R⁶ or R, wherein W is -C(R⁶)₂O-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)₂N(R⁶)CO-, -C(R⁶)₂N(R⁶)C(O)O-, or -CON(R⁶)-, and R is an optionally substituted group selected from C₁₋₆ aliphatic or phenyl, or R² and R^{2'} are taken together with their intervening atoms to form a substituted or unsubstitutedbenzo, pyrido, pyrimido, or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula III have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^x and R^y are taken together with their intervening atoms to form a benzo ring or a 5-7 membered carbocyclo ring optionally substituted with -R, oxo, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic),

$-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^4)CON(R^4)_2$,

$-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$; and

(c) each R^5 is independently selected from halo, oxo, CN, NO₂, $-N(R^4)_2$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$,
 5 $-SO_2N(R^4)_2$, $-N(R^4)SO_2R$, -SR, -OR, -C(O)R, or a substituted
 or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic.

Even more preferred compounds of formula III have one or more, and more preferably all, of the
 10 features selected from the group consisting of:

(a) R^x and R^y are taken together with their intervening atoms to form a benzo or 6-membered partially unsaturated carbocyclo ring optionally substituted with halo, CN, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, (C₁₋₆ alkyl)carbonyl,
 15 (C₁₋₆ alkyl)sulfonyl, mono- or dialkylamino, mono- or dialkylaminocarbonyl, mono- or dialkylaminocarbonyloxy, or 5-6 membered heteroaryl;

(b) each R^5 is independently selected from -halo, -CN, -oxo, -SR, -OR, $-N(R^4)_2$, -C(O)R, or a
 20 substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic; and

(c) R^2' is hydrogen and R^2 is selected from R^2' is hydrogen or methyl and R^2 is T-W-R⁶ or R, wherein W is
 $-C(R^6)_2O-$, $-C(R^6)_2N(R^6)-$, $-CO-$, $-CO_2-$, $-C(R^6)OC(O)-$,
 25 $-C(R^6)_2N(R^6)CO-$, or $-CON(R^6)-$, and R is an optionally substituted group selected from C₁₋₆ aliphatic or phenyl, or R^2 and R^2' are taken together with their intervening atoms to form a benzo, pyrido, or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, $-N(R^4)_2$, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), $-CO_2(C_{1-4} \text{ alkyl})$, -CN, $-SO_2(C_{1-4} \text{ alkyl})$, $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4} \text{ alkyl})$, $-NHC(O)(C_{1-4} \text{ alkyl})$,

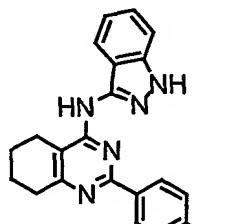
$-C(O)NH_2$, or $-CO(C_{1-4} \text{ alkyl})$, wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group.

Representative compounds of formula III are set forth in Table 2 below.

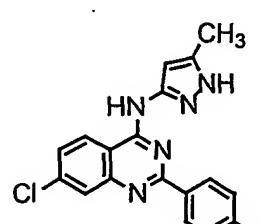
5

Table 2

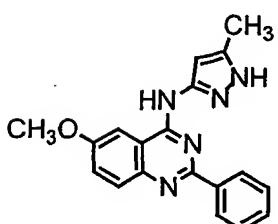
III-1



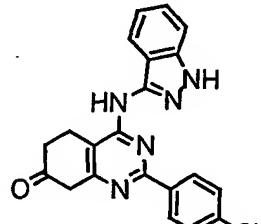
III-2



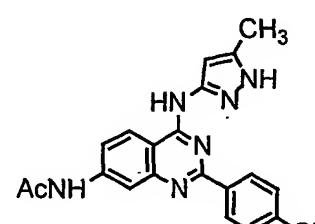
III-3



III-4



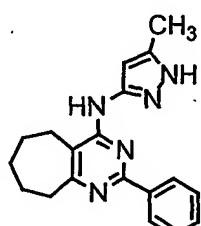
III-5



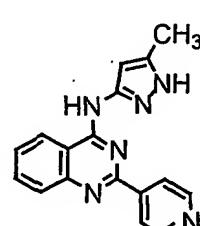
III-6



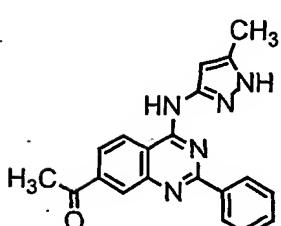
III-7



III-8



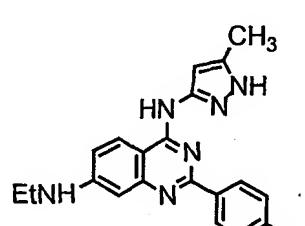
III-9



III-10

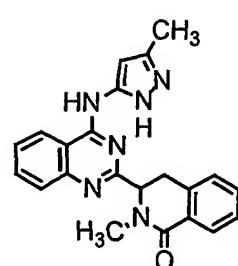
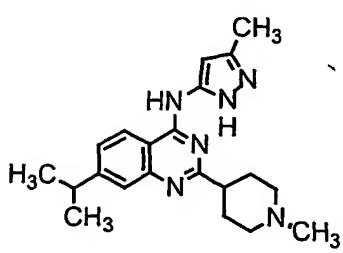
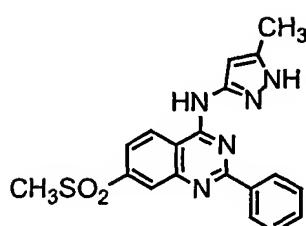
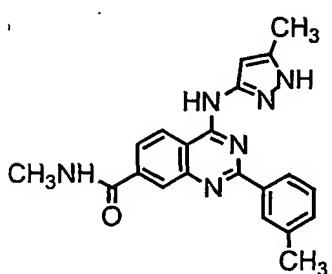
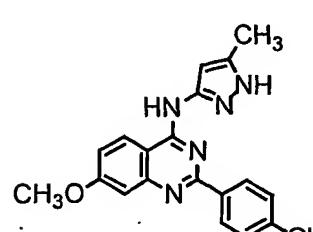
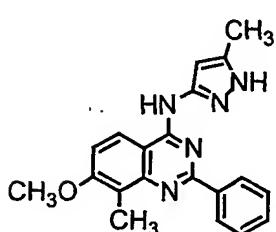
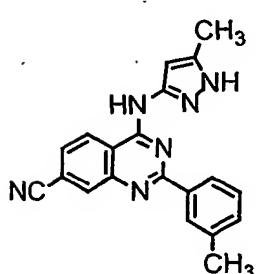
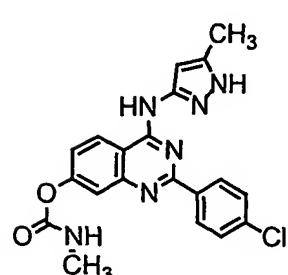
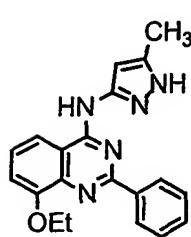
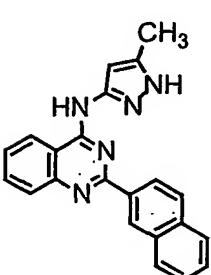
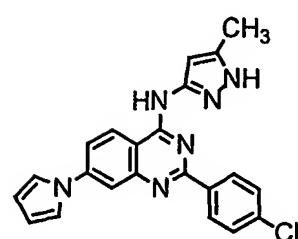
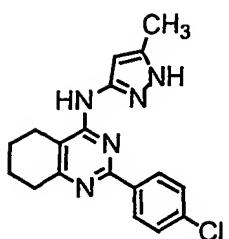
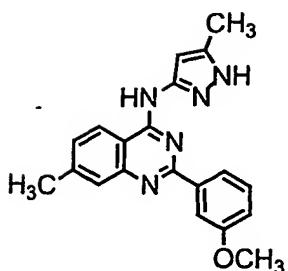


III-11

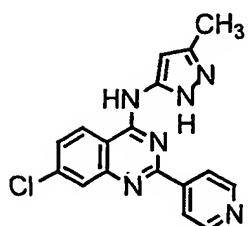


III-12

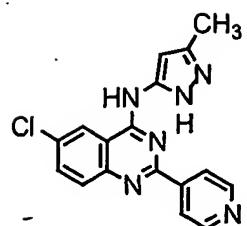
15



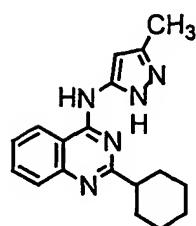
III-25



III-26

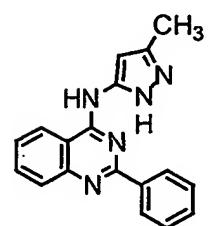


III-27

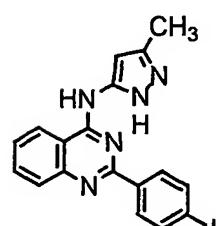


5

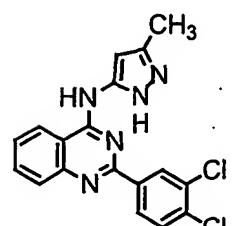
III-28



III-29

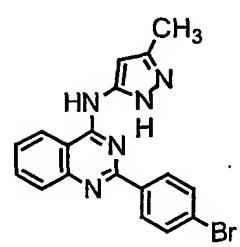


III-30



10

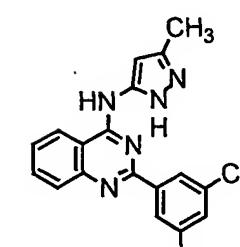
III-31



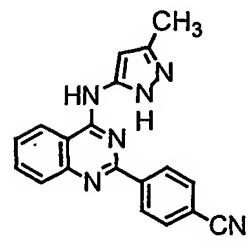
III-32



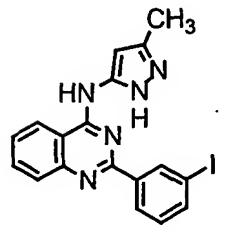
III-33



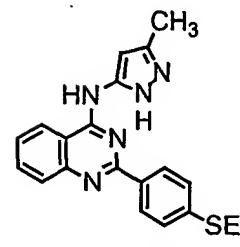
III-34



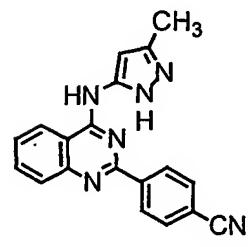
III-35



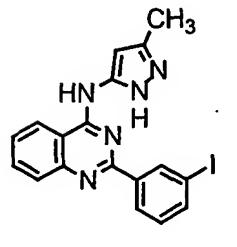
III-36



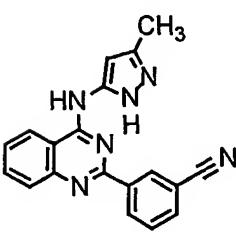
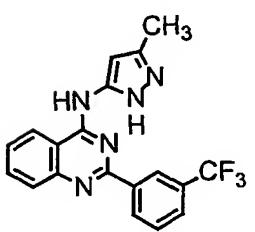
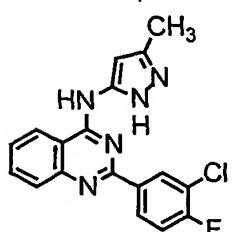
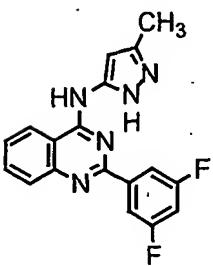
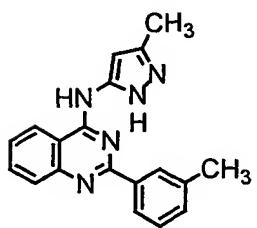
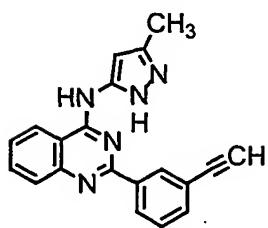
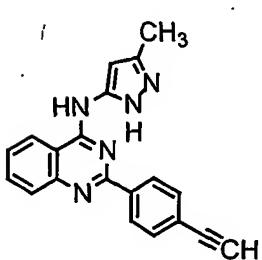
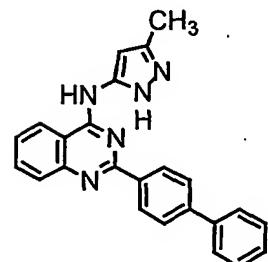
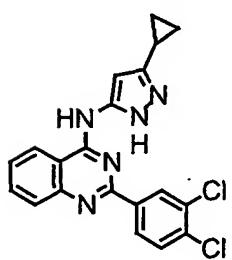
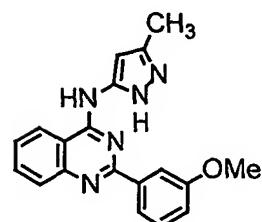
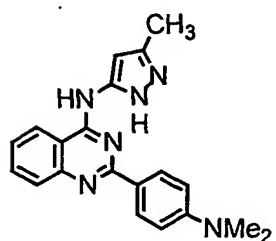
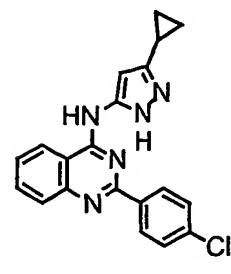
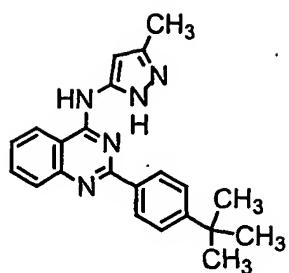
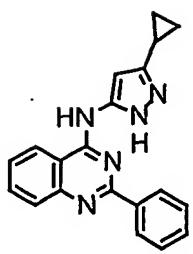
III-37

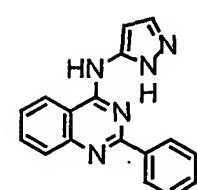
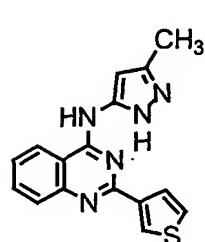
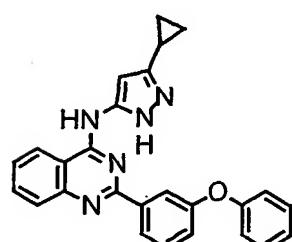
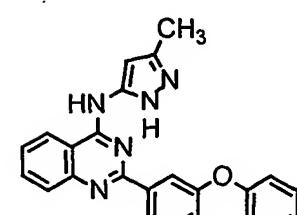
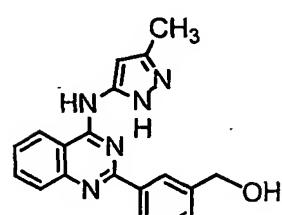
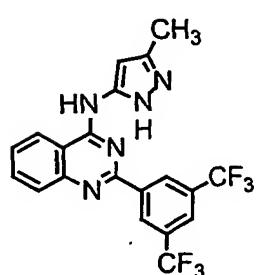
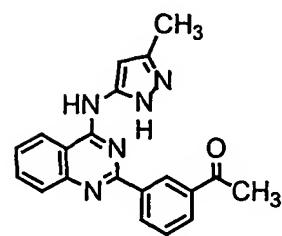
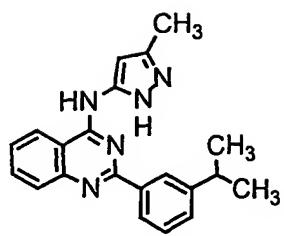


III-38

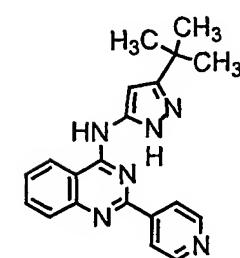
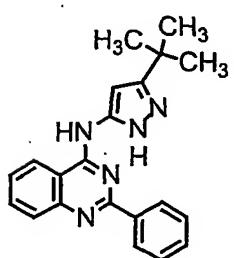
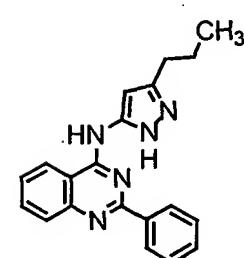
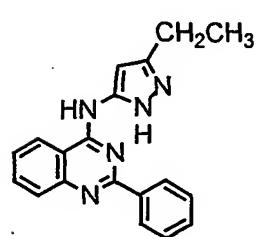
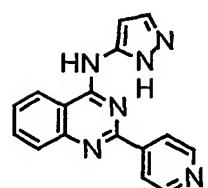


III-39



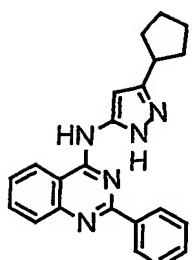


10

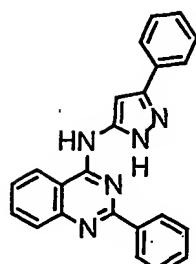


15

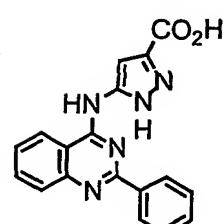
III-67



III-68



III-69

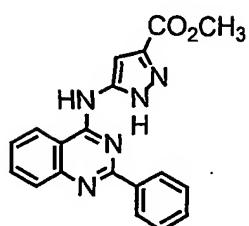


III-70

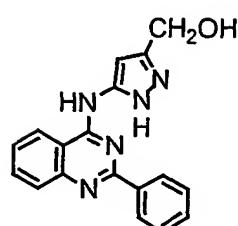
5

III-71

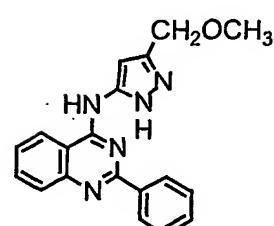
III-72



III-73

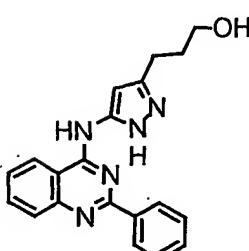


III-74

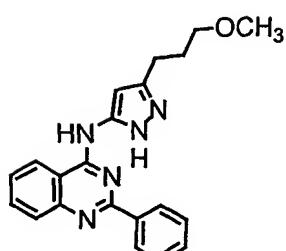


III-75

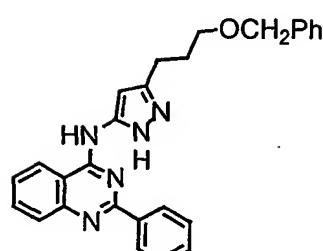
10



III-76

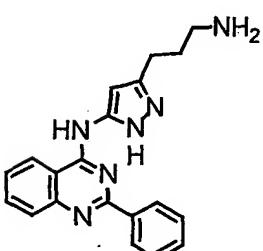


III-77

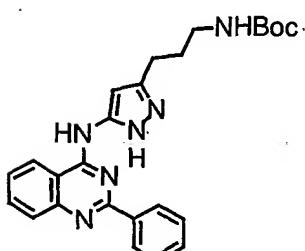


III-78

15



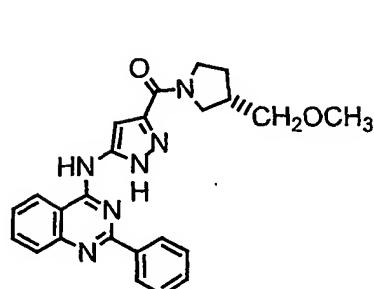
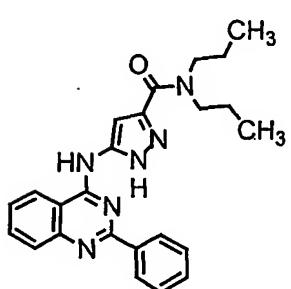
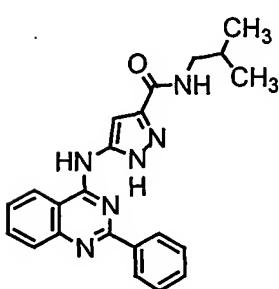
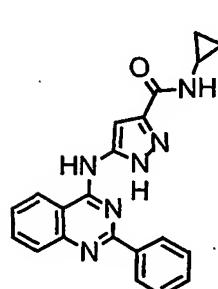
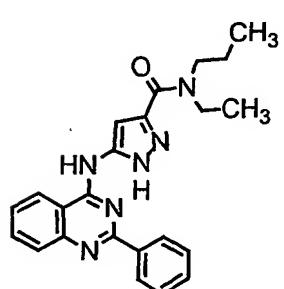
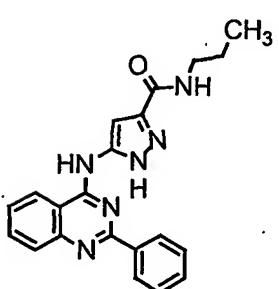
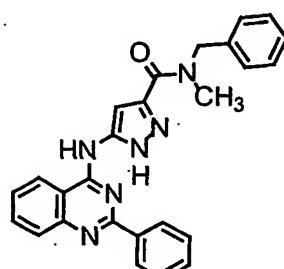
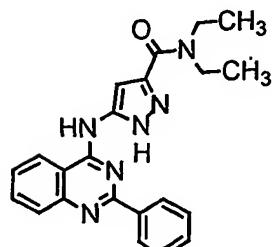
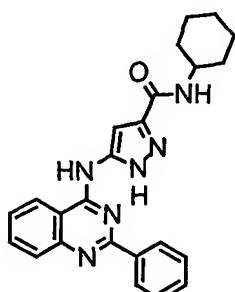
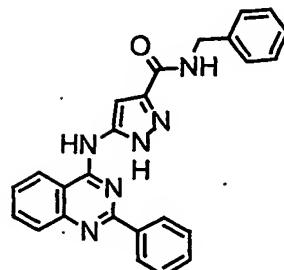
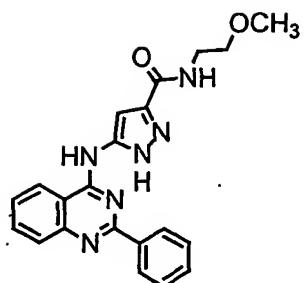
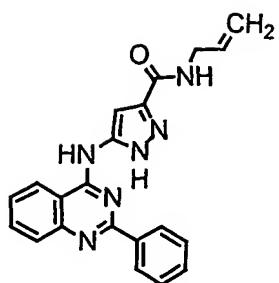
III-79

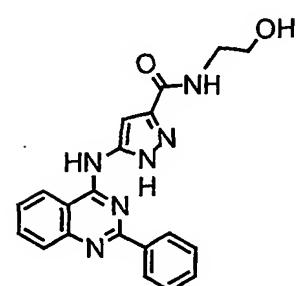
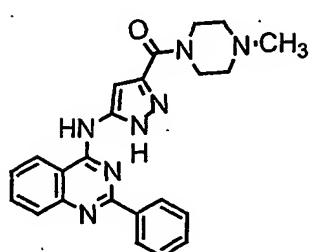
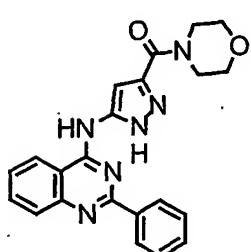
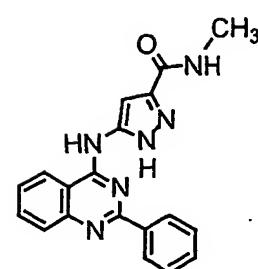
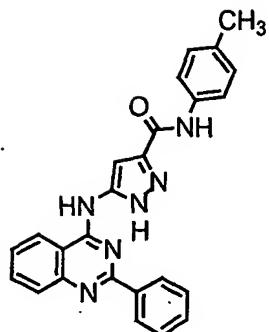
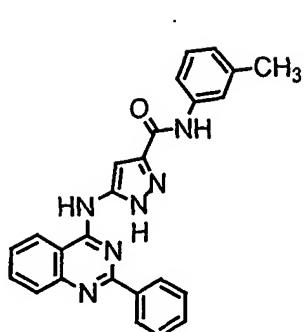


III-80

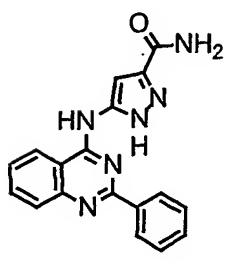


III-81

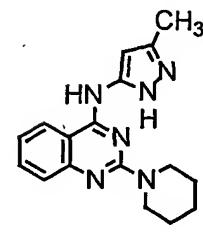
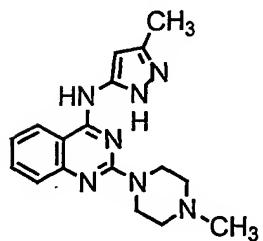
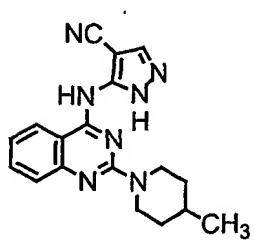
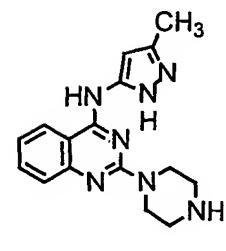




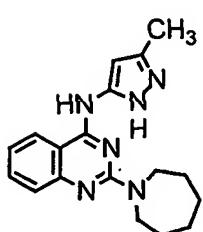
5



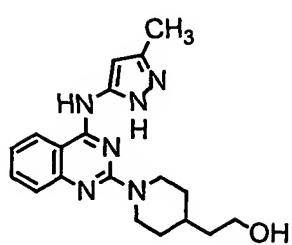
10



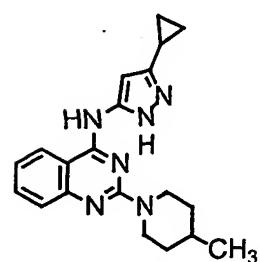
III-106



III-107



III-108

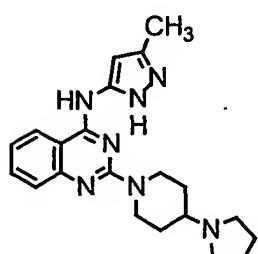


III-109

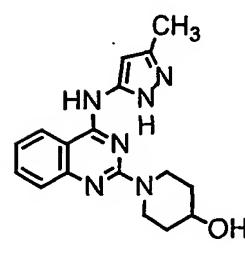
5



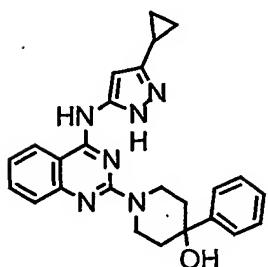
III-110



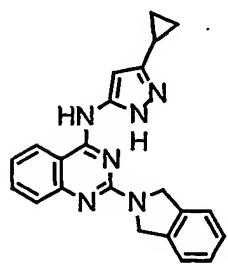
III-111



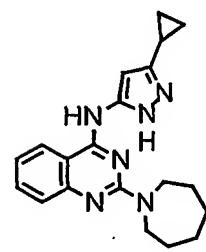
III-112



III-113

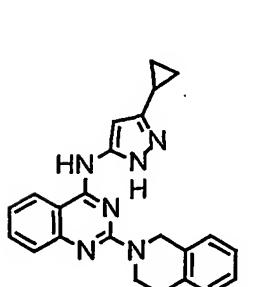


III-114

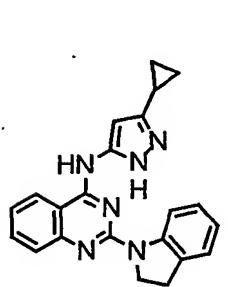


10

III-115



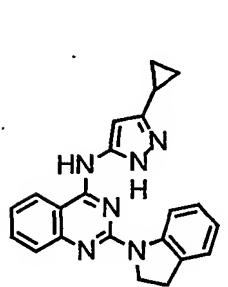
III-116



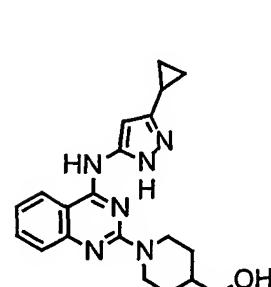
III-117

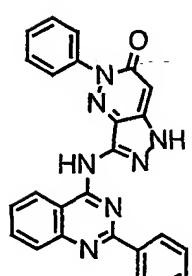
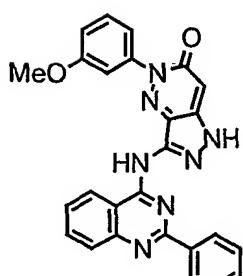
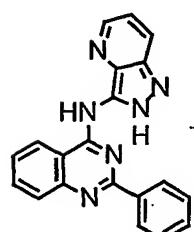
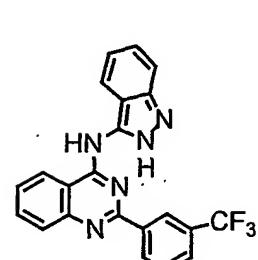
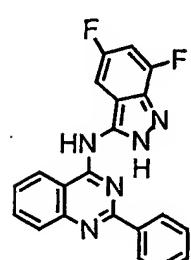
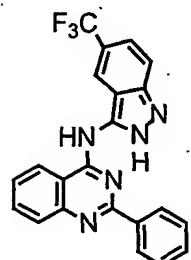
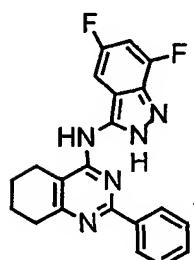
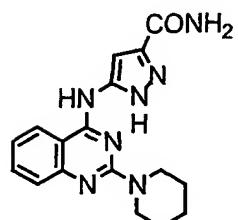
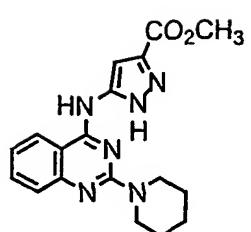
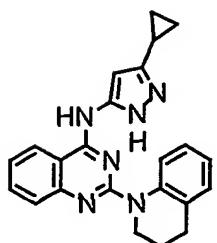


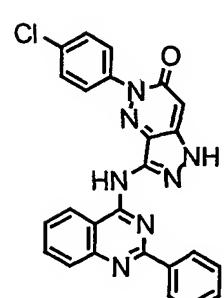
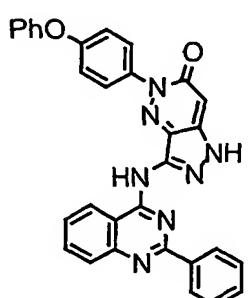
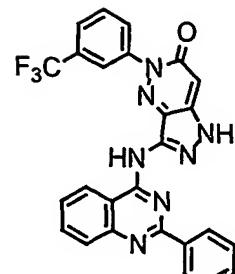
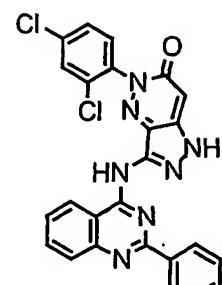
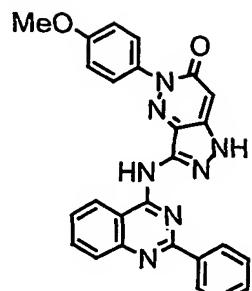
III-119



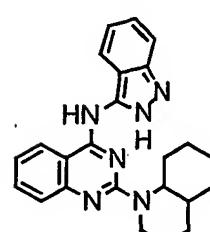
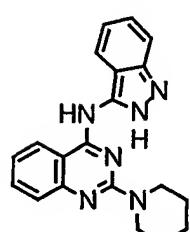
III-120



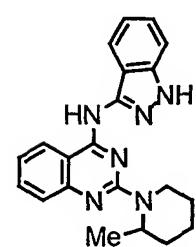
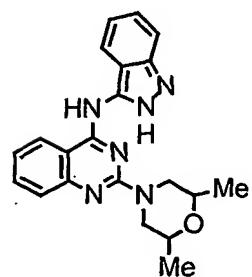




5



10



In another embodiment, this invention provides a composition comprising a compound of formula III and a pharmaceutically acceptable carrier.

One aspect of this invention relates to a
5 method of inhibiting GSK-3 activity in a patient,
comprising administering to the patient a therapeutically
effective amount of a composition comprising a compound
of formula III.

Another aspect relates to a method of treating
10 a disease that is alleviated by treatment with a GSK-3
inhibitor, said method comprising the step of
administering to a patient in need of such a treatment a
therapeutically effective amount of a composition
comprising a compound of formula III.

15 Another aspect relates to a method of enhancing
glycogen synthesis and/or lowering blood levels of
glucose in a patient in need thereof, comprising
administering to said patient a therapeutically effective
amount of a composition comprising a compound of formula
20 III. This method is especially useful for diabetic
patients.

Another aspect relates to a method of
inhibiting the production of hyperphosphorylated Tau
protein in a patient in need thereof, comprising
25 administering to said patient a therapeutically effective
amount of a composition comprising a compound of formula
III. This method is especially useful in halting or
slowing the progression of Alzheimer's disease.

Another aspect relates to a method of
30 inhibiting the phosphorylation of β -catenin in a patient
in need thereof, comprising administering to said patient
a therapeutically effective amount of a composition

comprising a compound of formula III. This method is especially useful for treating schizophrenia.

One aspect of this invention relates to a method of inhibiting Aurora activity in a patient,
5 comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula III.

Another aspect relates to a method of treating a disease that is alleviated by treatment with an Aurora
10 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula III. This method is especially useful for treating cancer, such as colon,
15 ovarian, and breast cancer.

One aspect of this invention relates to a method of inhibiting CDK-2 activity in a patient,
comprising administering to the patient a therapeutically effective amount of a composition comprising a compound
20 of formula III.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a CDK-2 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a
25 therapeutically effective amount of a composition comprising a compound of formula III. This method is especially useful for treating cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis,
30 alopecia, and autoimmune diseases such as rheumatoid arthritis.

One aspect of this invention relates to a method of inhibiting Src activity in a patient,

comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula III.

Another aspect relates to a method of treating
5. a disease that is alleviated by treatment with a Src inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula III. This method is
10 especially useful for treating hypercalcemia, osteoporosis, osteoarthritis, cancer, symptomatic treatment of bone metastasis, and Paget's disease.

Another method relates to inhibiting GSK-3, Aurora, CDK-2, or Src activity in a biological sample,
15 which method comprises contacting the biological sample with the GSK-3, Aurora, CDK-2, or Src inhibitor of formula III, or a pharmaceutical composition thereof, in an amount effective to inhibit GSK-3, Aurora, CDK-2, or Src.

20 Each of the aforementioned methods directed to the inhibition of GSK-3, Aurora, CDK-2, or Src, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula III, as described above.

25 Compounds of formula III, wherein R^{2'} is hydrogen and R^x and R^y are taken together with the pyrimidine ring to form an optionally substituted quinazoline ring system, are also inhibitors of ERK-2 and AKT protein kinases.

30 Accordingly, another method of this invention relates to a method of inhibiting ERK-2 or AKT activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition

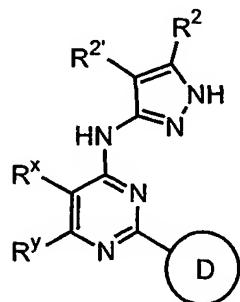
comprising a compound of formula III, wherein R^{2'} is hydrogen and R^x and R^y are taken together with the pyrimidine ring to form an optionally substituted quinazoline ring system.

5 Another aspect relates to a method of treating a disease that is alleviated by treatment with a ERK-2 or AKT inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition

10 comprising a compound of formula III, wherein R^{2'} is hydrogen and R^x and R^y are taken together with the pyrimidine ring to form an optionally substituted quinazoline ring system. This method is especially useful for treating cancer, stroke, hepatomegaly,

15 cardiovascular disease, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, restenosis, psoriasis, allergic disorders including asthma, inflammation, and neurological disorders.

Another embodiment of this invention relates to
20 compounds of formula IV:



IV

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

Ring D is a 5-7 membered monocyclic ring or 8-10 membered
25 bicyclic ring selected from aryl, heteroaryl,
heterocyclyl or carbocyclyl, said heteroaryl or

heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or -R⁵, and at any substitutable ring nitrogen by -R⁴,

5 provided that when Ring D is a six-membered aryl or heteroaryl ring, -R⁵ is hydrogen at each ortho carbon position of Ring D;

R^x and R^y are independently selected from T-R³, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 1-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring is optionally and independently substituted by T-R³, and any substitutable nitrogen on said ring is substituted by R⁴;

T is a valence bond or a C₁₋₄ alkylidene chain;

R² and R^{2'} are independently selected from -R, -T-W-R⁶, or R² and R^{2'} are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring containing 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein said fused ring is optionally substituted by up to three groups independently selected from halo, oxo,

10 -CN, -NO₂, -R⁷, or -V-R⁶;

15 R³ is selected from -R, -halo, =O, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆

aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or 5 heteroaryl ring;

each R⁵ is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, 10 -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, 15 -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

20 W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, 25 -C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;

each R⁶ is independently selected from hydrogen or an optionally substituted C₁₋₄ aliphatic group, or two R⁶ groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring; and 30

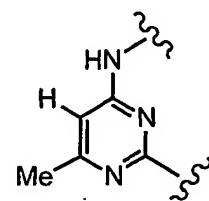
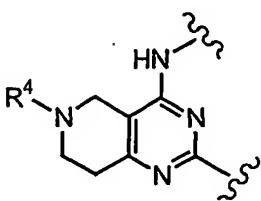
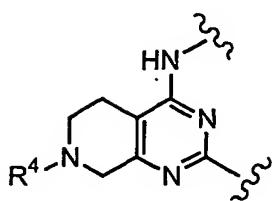
each R⁷ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl ring or 5 heteroaryl.

Preferred formula IV Ring D monocyclic rings include substituted and unsubstituted phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, and morpholinyl rings. Preferred formula IV 10 Ring D bicyclic rings include 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, and naphthyl. Examples of more preferred Ring D bicyclic rings include naphthyl and 15 isoquinolinyl.

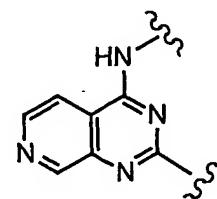
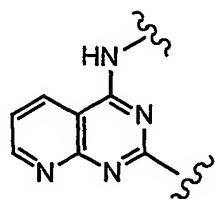
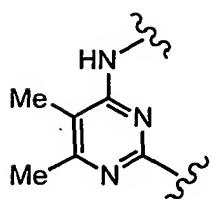
Preferred substituents on Ring D of formula IV include halo, oxo, CN, -NO₂, -N(R⁴)₂, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -SR, -OR, -C(O)R, or substituted or unsubstituted group selected from 5-6 20 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. More preferred R⁵ substituents include -halo, -CN, -oxo, -SR, -OR, -N(R⁴)₂, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. Examples of Ring D substituents 25 include -OH, phenyl, methyl, CH₂OH, CH₂CH₂OH, pyrrolidinyl, OPh, CF₃, C≡CH, Cl, Br, F, I, NH₂, C(O)CH₃, i-propyl, tert-butyl, SET, OMe, N(Me)₂, methylene dioxy, and ethylene dioxy.

When the R^x and R^y groups of formula IV are 30 taken together to form a fused ring, preferred R^x/R^y rings include a 5-, 6-, 7-, or 8-membered unsaturated or partially unsaturated ring having 1-2 heteroatoms. This provides a bicyclic ring system containing the pyrimidine

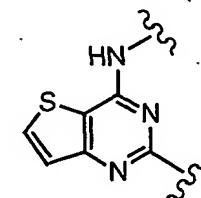
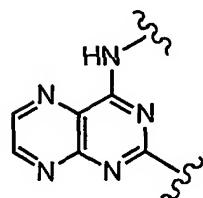
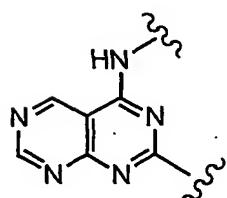
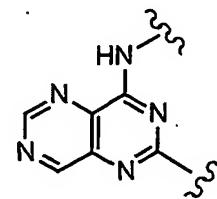
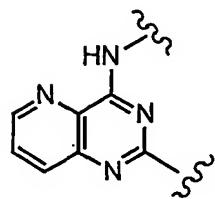
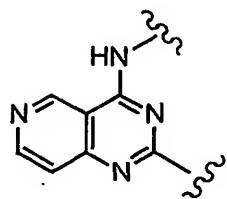
ring. Examples of preferred pyrimidine ring systems of formula IV are the mono- and bicyclic systems shown below.



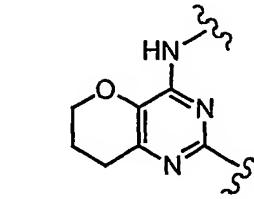
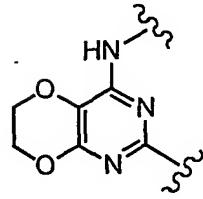
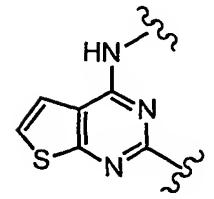
5

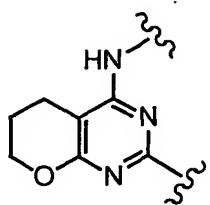


10

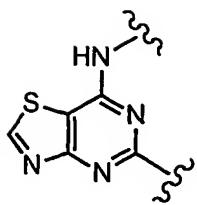


15

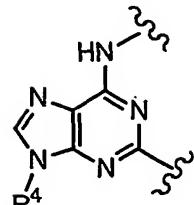




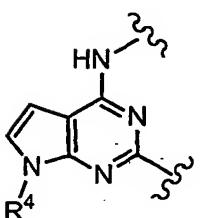
IV-U



IV-V

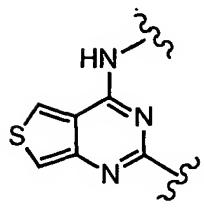


IV-W

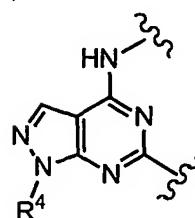


5

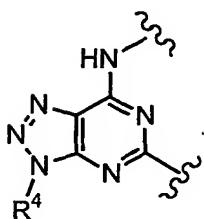
IV-X



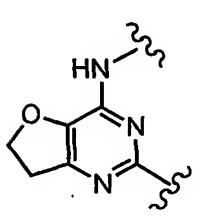
IV-Y



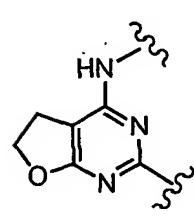
IV-Z



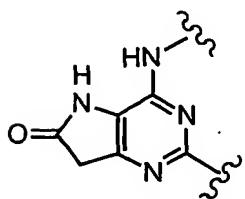
IV-AA



IV-BB



IV-CC



10

IV-DD

More preferred pyrimidine ring systems of formula IV include IV-E, IV-G, IV-H, IV-J, IV-K, IV-L, 15 IV-M, IV-T, and IV-U.

In the monocyclic pyrimidine ring system of formula IV, preferred R^x groups include hydrogen, amino, nitro, alkyl- or dialkylamino, acetamido, or a C₁₋₄ aliphatic group such as methyl, ethyl, cyclopropyl, 20 isopropyl or t-butyl. Preferred R^y groups include T-R³ wherein T is a valence bond or a methylene, and R³ is -R,

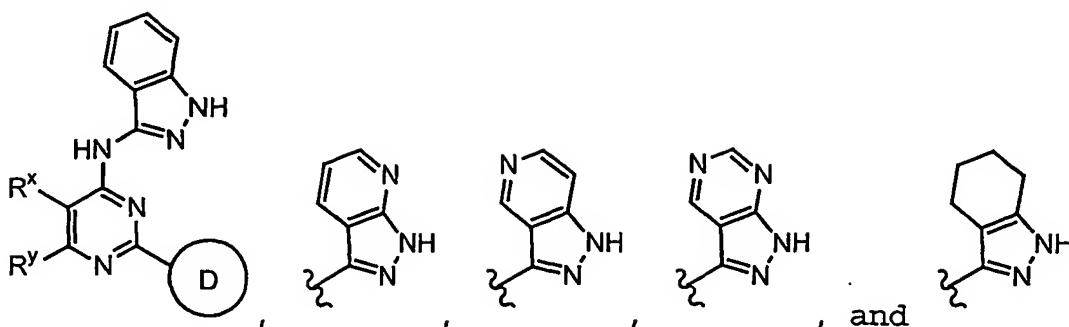
-N(R⁴)₂, or -OR. When R³ is -R or -OR, a preferred R is an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring. Examples of preferred R^Y groups

5 include 2-pyridyl, 4-pyridyl, piperidinyl, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or dialkylamino, acetamido, optionally substituted phenyl such as phenyl, methoxyphenyl, trimethoxyphenyl, or halo-substituted phenyl, and methoxymethyl.

10 In the bicyclic pyrimidine ring system of formula IV, the ring formed when R^X and R^Y are taken together may be substituted or unsubstituted. Suitable substituents include -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, 15 -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, wherein R and R⁴ are as defined above for compounds of formula IV. Preferred R^X/R^Y ring substituents include -halo, -R, -OR, -COR, -CO₂R, 20 -CON(R⁴)₂, -CN, or -N(R⁴)₂ wherein R is a substituted or unsubstituted C₁₋₆ aliphatic group.

The R² and R^{2'} groups of formula IV may be taken together to form a fused ring, thus providing a bicyclic 25 ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring. These are exemplified in the following formula IV compounds having a pyrazole-containing bicyclic ring system:

30



Preferred substituents on the R²/R^{2'} fused ring of formula IV include one or more of the following:

- 5 -halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, and -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group. Preferably,
- 10 the (C₁₋₄ alkyl) group is methyl.

When the pyrazole ring system of formula IV is monocyclic, preferred R² groups include hydrogen, a substituted or unsubstituted group selected from aryl, heteroaryl, or a C₁₋₆ aliphatic group. Examples of such preferred R² groups include methyl, t-butyl, -CH₂OCH₃, cyclopropyl, furanyl, thienyl, and phenyl. A preferred R^{2'} group is hydrogen.

Preferred formula IV compounds have one or more, and more preferably all, of the features selected from the group consisting of:

- (a) Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^x is hydrogen or C_{1-4} aliphatic and R^y is $T-R^3$, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted 5-7 membered unsaturated or partially unsaturated ring having 1-2 ring heteroatoms; and

(c) R^2' is hydrogen or methyl and R^2 is $T-W-R^6$ or R , wherein W is $-C(R^6)_2O-$, $-C(R^6)_2N(R^6)-$, $-CO-$, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, or $-CON(R^6)-$, and R is an optionally substituted group selected from C_{1-6} aliphatic or phenyl, or R^2 and R^2' are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido, or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula IV have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^x is hydrogen or methyl and R^y is $-R$, $N(R^4)_2$, or $-OR$, or R^x and R^y are taken together with their intervening atoms to form a 5-7 membered unsaturated or partially unsaturated ring having 1-2 ring nitrogens, wherein said ring is optionally substituted with $-R$, halo, oxo, $-OR$, $-C(=O)R$, $-CO_2R$, $-COCOR$, $-NO_2$, $-CN$, $-S(O)R$, $-SO_2R$, $-SR$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$ (optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$; and

(c) each R⁵ is independently selected from halo, oxo, CN, NO₂, -N(R⁴)₂, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -SR, -OR, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic.

Even more preferred compounds of formula IV have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R^x and R^y are taken together with their intervening atoms to form a 6-membered unsaturated or partially unsaturated ring having 1-2 ring nitrogens, optionally substituted with halo, CN, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, (C₁₋₆ alkyl)carbonyl, (C₁₋₆ alkyl)sulfonyl, mono- or dialkylamino, mono- or dialkylaminocarbonyl, mono- or 15 dialkylaminocarbonyloxy, or 5-6 membered heteroaryl;

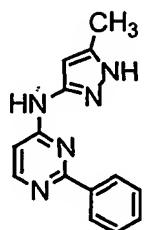
(b) each R⁵ is independently selected from -halo, -CN, -oxo, -SR, -OR, -N(R⁴)₂, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic; and

(c) R^{2'} is hydrogen and R² is T-W-R⁶ or R, wherein W is -C(R⁶)₂O-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)₂N(R⁶)CO-, or -CON(R⁶)-, and R is an optionally substituted group selected from C₁₋₆ aliphatic or phenyl, or R² and R^{2'} are taken together with their intervening atoms to form a benzo, pyrido, or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, oxo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, or -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group.

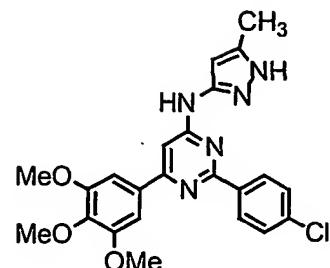
Representative compounds of formula IV are set forth in Table 3 below.

Table 3.

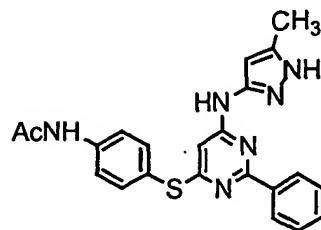
5



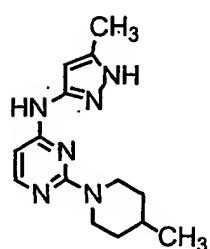
IV-1



IV-2

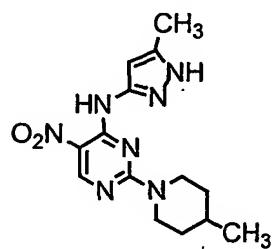


IV-3

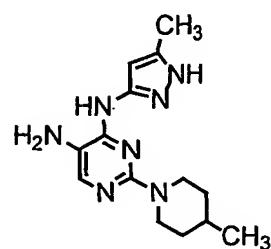


10

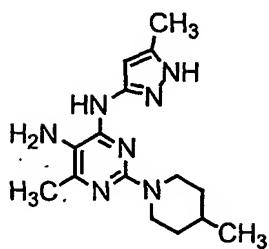
IV-4



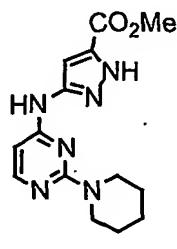
IV-5



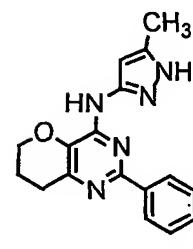
IV-6



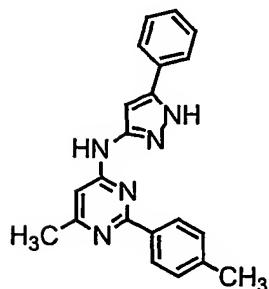
IV-7



IV-8

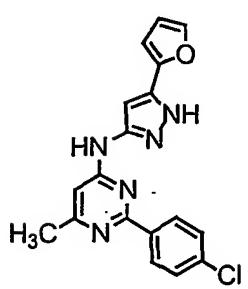


IV-9

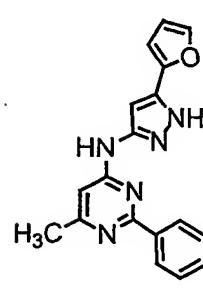


15

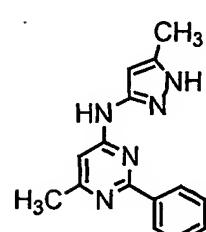
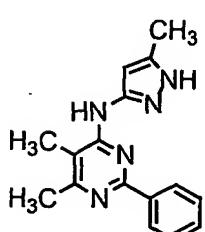
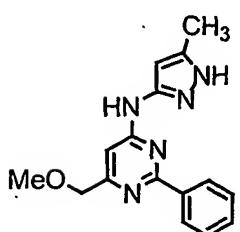
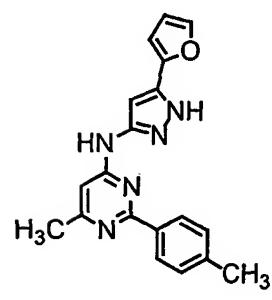
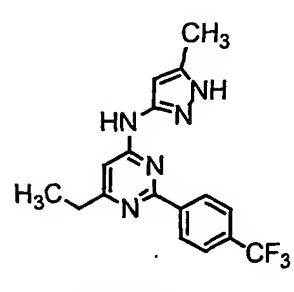
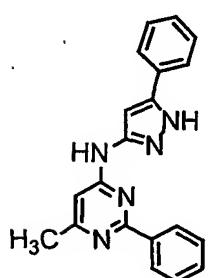
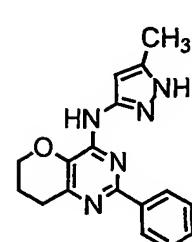
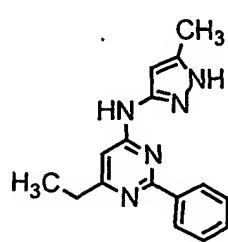
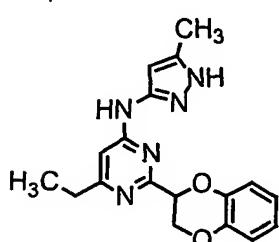
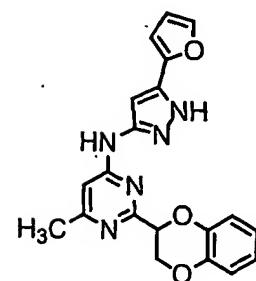
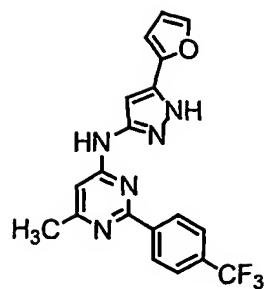
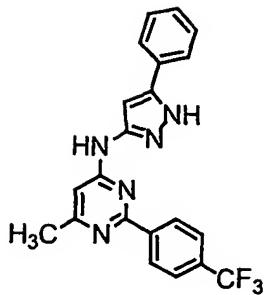
IV-10



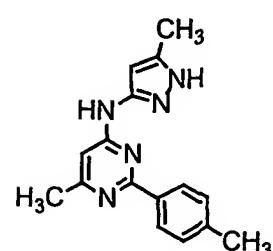
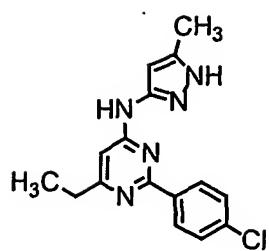
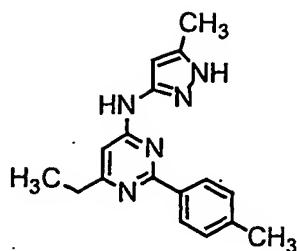
IV-11



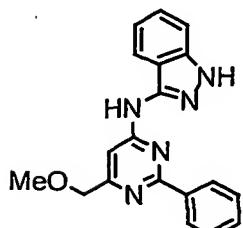
IV-12



10



5

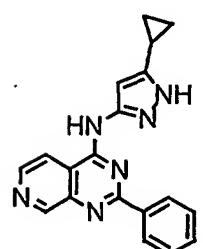
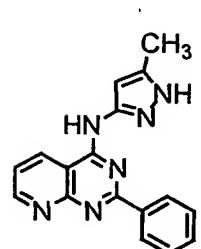


10

In another embodiment, this invention provides a composition comprising a compound of formula IV and a pharmaceutically acceptable carrier.

One aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula IV.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a GSK-3 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a



therapeutically effective amount of a composition comprising a compound of formula IV.

Another aspect relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula IV. This method is especially useful for diabetic patients.

10 Another aspect relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula IV. This method is especially useful in halting or 15 slowing the progression of Alzheimer's disease.

Another aspect relates to a method of inhibiting the phosphorylation of β -catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula IV. This method is especially useful for treating schizophrenia.

One aspect of this invention relates to a method of inhibiting Aurora activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula IV.

Another aspect relates to a method of treating a disease that is alleviated by treatment with an Aurora inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula IV. This method is

especially useful for treating cancer, such as colon, ovarian, and breast cancer.

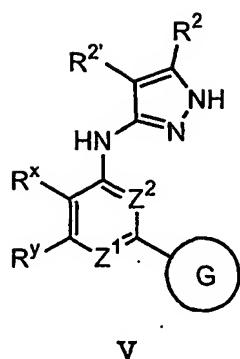
One aspect of this invention relates to a method of inhibiting CDK-2 activity in a patient, 5 comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula IV.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a CDK-2 10 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula IV. This method is especially useful for treating cancer, Alzheimer's 15 disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid arthritis.

Another method relates to inhibiting GSK-3, 20 Aurora, or CDK-2 activity in a biological sample, which method comprises contacting the biological sample with the GSK-3 or Aurora inhibitor of formula IV, or a pharmaceutical composition thereof, in an amount effective to inhibit GSK-3, Aurora or CDK-2.

25 Each of the aforementioned methods directed to the inhibition of GSK-3, Aurora or CDK-2, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula IV, as described above.

30 Another embodiment of this invention relates to compounds of formula V:



or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

Z^1 is N, CR^a, or CH and Z^2 is N or CH, provided that one of Z^1 and Z^2 is nitrogen;

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, 5 pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring,

wherein said Ring C has one or two ortho substituents independently selected from -R¹, any substitutable non-ortho carbon position on Ring C is independently substituted by -R⁵, and two adjacent substituents on

10 Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or -R⁸;

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected

20 from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or -R⁵, and at any substitutable ring nitrogen by -R⁴, provided that when Ring D is a six-membered aryl or

heteroaryl ring, -R⁵ is hydrogen at each ortho carbon position of Ring D;

R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or -R⁸, said C₁₋₆ aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R¹ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

10 R^x and R^y are independently selected from T-R³, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or T-R³, and any substitutable nitrogen on said ring formed by R^x and R^y is substituted by R⁴;

T is a valence bond or a C₁₋₄ alkylidene chain;

15 R² and R^{2'} are independently selected from -R, -T-W-R⁶, or R² and R^{2'} are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R² and R^{2'} is substituted by halo, oxo, -CN, -NO₂, -R⁷, or -V-R⁶, and any substitutable nitrogen on said ring formed by R² and R^{2'} is substituted by R⁴;

20 R³ is selected from -R, -halo, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR,

-N(R⁷)CO₂(optionally substituted C₁₋₆ aliphatic),
 -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂,
 -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁷)₂;

each R is independently selected from hydrogen or an
 optionally substituted group selected from C₁₋₆
 aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10
 ring atoms, or a heterocyclyl ring having 5-10 ring
 atoms;

each R⁴ is independently selected from -R⁷, -COR⁷,
 -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂,
 or -SO₂R⁷, or two R⁴ on the same nitrogen are taken
 together to form a 5-8 membered heterocyclyl or
 5 heteroaryl ring;

each R⁵ is independently selected from -R, halo, -OR,
 -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR,
 -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR,
 -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic),
 10 -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂,
 -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, or R⁵ and
 an adjacent substituent taken together with their
 intervening atoms form said ring fused to Ring C;
 V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-,
 15 -N(R⁶)-, -CO-, -CO₂- , -N(R⁶)CO-, -N(R⁶)C(O)O-,
 -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-,
 -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-,
 -C(R⁶)₂SO-, -C(R⁶)₂SO₂- , -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-,
 -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-,
 20 -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or
 -C(R⁶)₂N(R⁶)CON(R⁶)- ;
 W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂- ,
 -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂- ,
 -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-,
 25 -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-,

-C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-,

-C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;

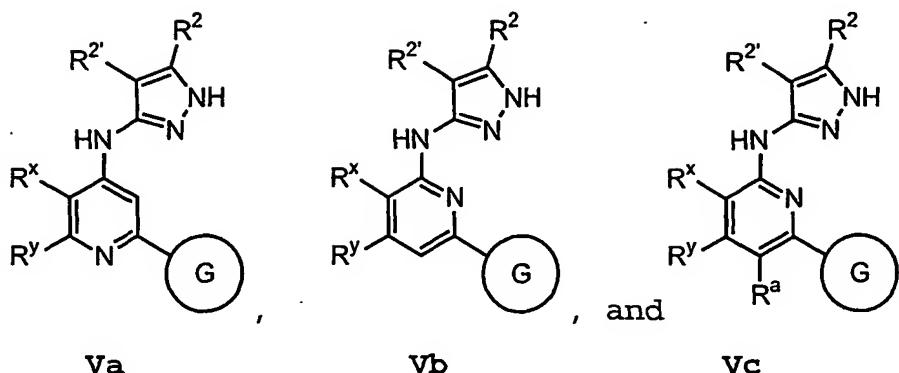
each R⁶ is independently selected from hydrogen, an
optionally substituted C₁₋₄ aliphatic group, or two R⁶
5 groups on the same nitrogen atom are taken together
with the nitrogen atom to form a 5-6 membered
heterocyclyl or heteroaryl ring;

each R⁷ is independently selected from hydrogen or an
optionally substituted C₁₋₆ aliphatic group, or two R⁷
10 on the same nitrogen are taken together with the
nitrogen to form a 5-8 membered heterocyclyl or
heteroaryl ring;

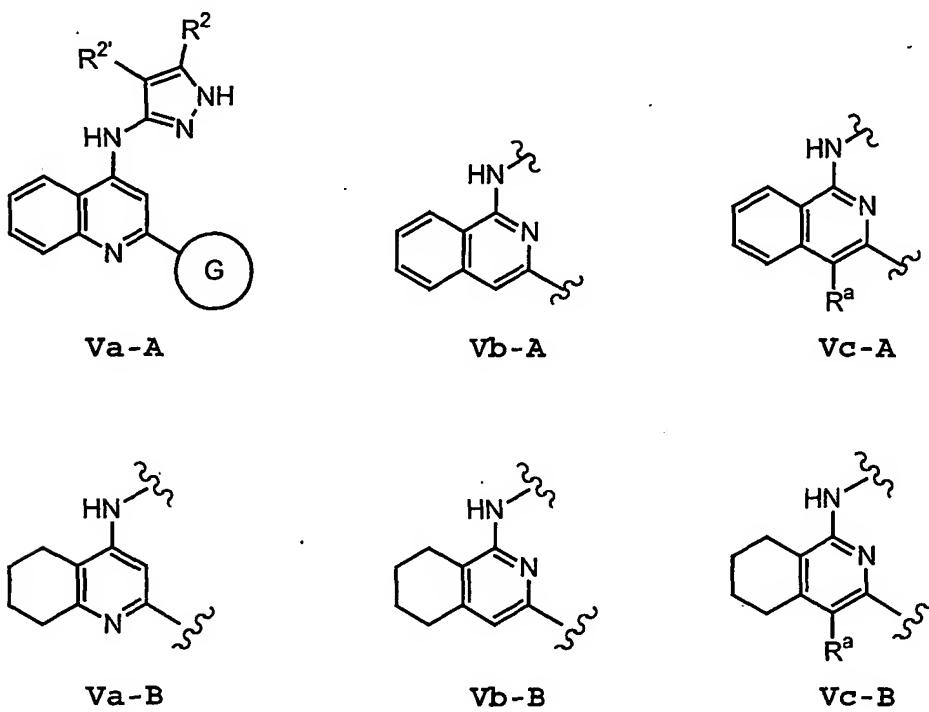
each R⁸ is independently selected from an optionally
substituted C₁₋₄ aliphatic group, -OR⁶, -SR⁶, -COR⁶,
15 -SO₂R⁶, -N(R⁶)₂, -N(R⁶)N(R⁶)₂, -CN, -NO₂, -CON(R⁶)₂, or
-CO₂R⁶; and

R^a is selected from halo, -OR, -C(=O)R, -CO₂R, -COCOR,
-NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂,
-SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally
20 substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂,
-C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R,
-OC(=O)N(R⁴)₂, or an optionally substituted group
selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl
ring having 5-10 ring atoms, or a heterocyclyl ring
25 having 5-10 ring atoms.

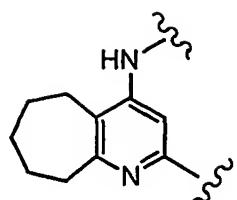
Compounds of formula V may be represented by
specifying Z¹ and Z² as shown below:



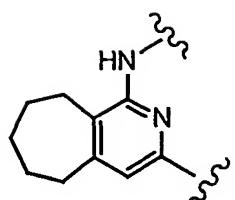
When the R^x and R^y groups of formula V are taken
 5 together to form a fused ring, preferred R^x/R^y rings
 include a 5-, 6-, 7-, or 8-membered unsaturated or
 partially unsaturated ring having 0-2 heteroatoms,
 wherein said R^x/R^y ring is optionally substituted. This
 provides a bicyclic ring system containing a pyridine
 10 ring. Examples of preferred bicyclic ring systems of
 formula V are shown below.



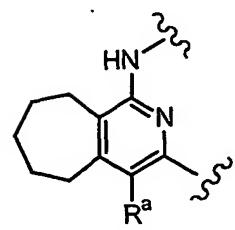
15



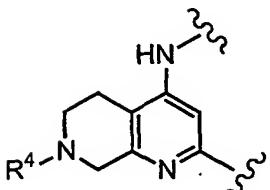
Vb-C



Va-C

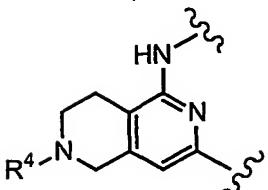


Vc-C

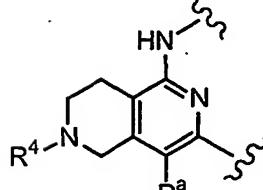


5

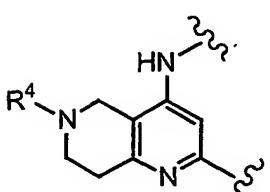
Va-D



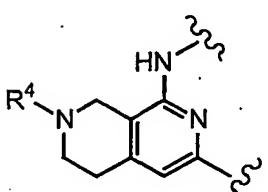
Vb-D



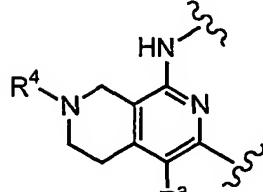
Vc-D



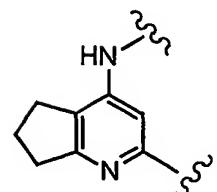
Va-E



Vb-E

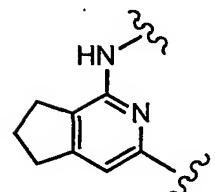


Vc-E

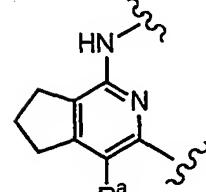


10

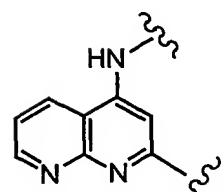
Va-F



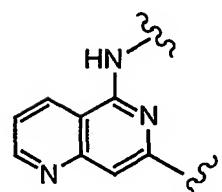
Vb-F



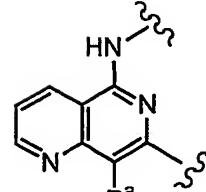
Vc-F



Va-J

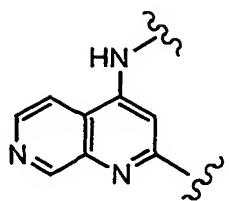


Vb-J

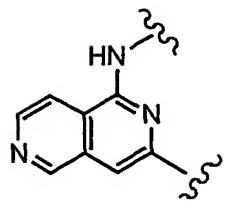


Vc-J

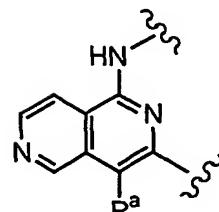
15



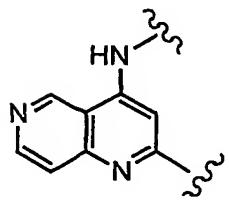
Vb-K



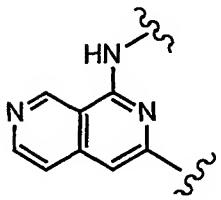
Vc-K



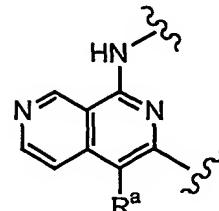
Va-K



Vb-L

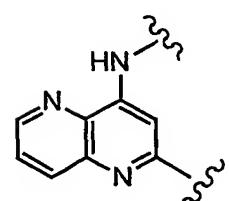


Vc-L

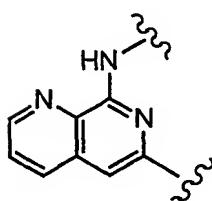


Va-L

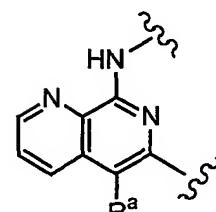
5



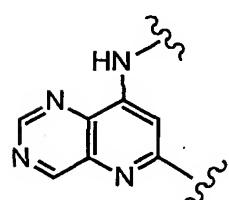
Vb-M



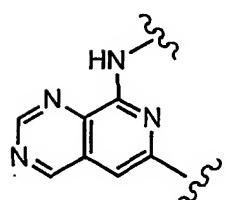
Vc-M



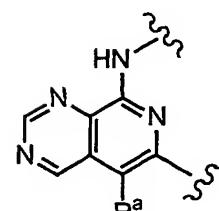
Va-M



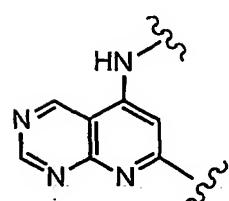
Vb-N



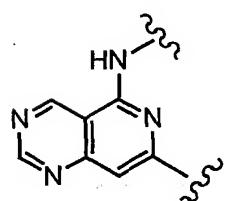
Vc-N



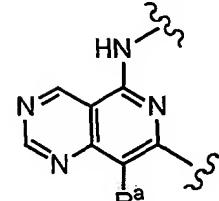
10

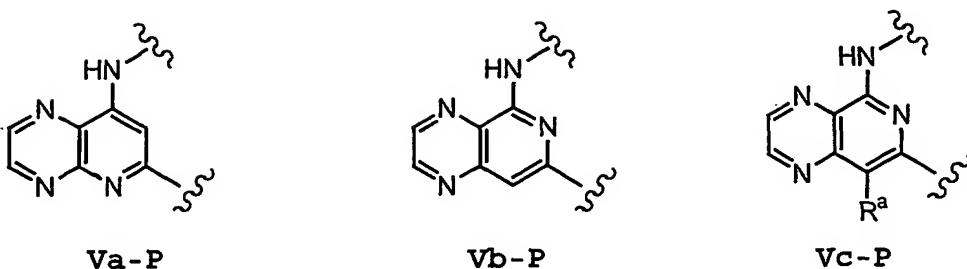


Vb-O



Vc-O





More preferred bicyclic ring systems of formula

5 V include Va-A, Vb-A, Vc-A, Va-B, Vb-B, Vc-B, Va-D, Vb-D,
Vc-D, Va-E, Vb-E, Vc-E, Va-J, Vb-J, Vc-J, Va-K, Vb-K,
Vc-K, Va-L, Vb-L, Vc-L, Va-M, Vb-M, and Vc-M, most
preferably Va-A, Vb-A, Vc-A, Va-B, Vb-B, and Vc-B.

In the monocyclic pyridine ring system of
10 formula V, preferred R^x groups include hydrogen, alkyl- or
dialkylamino, acetamido, or a C₁₋₄ aliphatic group such as
methyl, ethyl, cyclopropyl, isopropyl or t-butyl.
Preferred R^y groups include T-R³ wherein T is a valence
bond or a methylene, and R³ is -R, -N(R⁴)₂, or -OR. When
15 R³ is -R or -OR, a preferred R is an optionally
substituted group selected from C₁₋₆ aliphatic, phenyl, or
a 5-6 membered heteroaryl or heterocyclyl ring. Examples
of preferred R^y include 2-pyridyl, 4-pyridyl, piperidinyl,
methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or
20 dialkylamino, acetamido, optionally substituted phenyl
such as phenyl or halo-substituted phenyl, and
methoxymethyl.

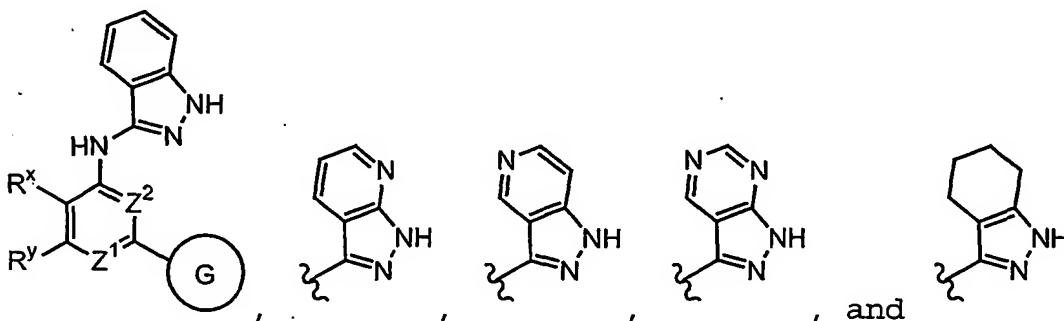
In the bicyclic ring system of formula V, the
ring formed when R^x and R^y are taken together may be
25 substituted or unsubstituted. Suitable substituents
include -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN,
-S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂,
-OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆
aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR,
30 -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or

$-\text{OC}(=\text{O})\text{N}(\text{R}^4)_2$, wherein R and R^4 are as defined above.

Preferred R^x/R^y ring substituents include -halo, -R, -OR, -COR, - CO_2R , - $\text{CON}(\text{R}^4)_2$, -CN, or - $\text{N}(\text{R}^4)_2$ wherein R is an optionally substituted C_{1-6} aliphatic group.

5 The R^2 and $\text{R}^{2'}$ groups of formula V may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring. These are

10 exemplified in the following formula V compounds having a pyrazole-containing bicyclic ring system:



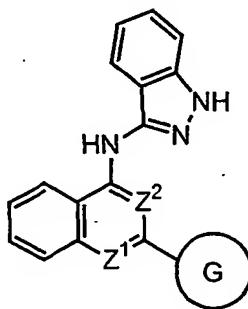
15 Preferred substituents on the $\text{R}^2/\text{R}^{2'}$ fused ring of formula V include one or more of the following: -halo, $-\text{N}(\text{R}^4)_2$, $-\text{C}_{1-4}$ alkyl, $-\text{C}_{1-4}$ haloalkyl, $-\text{NO}_2$, $-\text{O}(\text{C}_{1-4}\text{ alkyl})$, $-\text{CO}_2(\text{C}_{1-4}\text{ alkyl})$, -CN, $-\text{SO}_2(\text{C}_{1-4}\text{ alkyl})$, $-\text{SO}_2\text{NH}_2$, $-\text{OC}(\text{O})\text{NH}_2$, $-\text{NH}_2\text{SO}_2(\text{C}_{1-4}\text{ alkyl})$, $-\text{NHC}(\text{O})(\text{C}_{1-4}\text{ alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, and $-\text{CO}(\text{C}_{1-4}\text{ alkyl})$, wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C_{1-4} alkyl) group is methyl.

20 When the pyrazole ring system is monocyclic, preferred R^2 groups include hydrogen, C_{1-4} aliphatic, alkoxy carbonyl, (un)substituted phenyl, hydroxyalkyl, alkoxyalkyl, aminocarbonyl, mono- or dialkylaminocarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonyl, and (N-

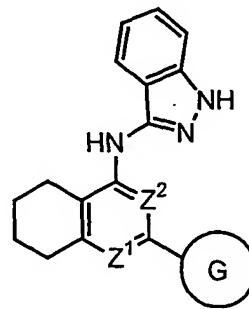
heterocyclyl) carbonyl. Examples of such preferred R² substituents include methyl, cyclopropyl, ethyl, isopropyl, propyl, t-butyl, cyclopentyl, phenyl, CO₂H, CO₂CH₃, CH₂OH, CH₂OCH₃, CH₂CH₂CH₂OH, CH₂CH₂CH₂OCH₃,

5 CH₂CH₂CH₂OCH₂Ph, CH₂CH₂CH₂NH₂, CH₂CH₂CH₂NHCOOC(CH₃)₃, CONHCH(CH₃)₂, CONHCH₂CH=CH₂, CONHCH₂CH₂OCH₃, CONHCH₂Ph, CONH(cyclohexyl), CON(Et)₂, CON(CH₃)CH₂Ph, CONH(n-C₃H₇), CON(Et)CH₂CH₂CH₃, CONHCH₂CH(CH₃)₂, CON(n-C₃H₇)₂, CO(3-methoxymethylpyrrolidin-1-yl), CONH(3-tolyl), CONH(4-tolyl), CONHCH₃, CO(morpholin-1-yl), CO(4-methylpiperazin-1-yl), CONHCH₂CH₂OH, CONH₂, and CO(piperidin-1-yl). A preferred R²' group is hydrogen.

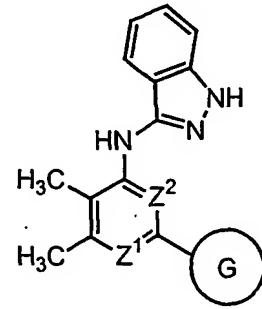
More preferred ring systems of formula V are the following, which may be substituted as described above, wherein R² and R²' are taken together with the pyrazole ring to form an optionally substituted indazole ring; and R^x and R^y are each methyl, or R^x and R^y are taken together with the pyridine ring to form an optionally substituted quinoline, isoquinoline, tetrahydroquinoline or tetrahydroisoquinoline ring:



V-Aa



V-Ba



V-Ha

When G is Ring C, preferred formula V Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring.

Such rings preferably are fused at ortho and meta positions of Ring C. Examples of preferred bicyclic Ring C systems include naphthyl and isoquinolinyl. Preferred R¹ groups include -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶. When R¹ is an optionally substituted C₁₋₆ aliphatic group, the most preferred optional substituents are halogen. Examples of preferred R¹ groups include -CF₃, -Cl, -F, -CN, -COCH₃, -OCH₃, -OH, -CH₂CH₃, -OCH₂CH₃, -CH₃, -CF₂CH₃, cyclohexyl, t-butyl, isopropyl, cyclopropyl, -C≡CH, -C≡C-CH₃, -SO₂CH₃, -SO₂NH₂, -N(CH₃)₂, -CO₂CH₃, -CONH₂, -NHCOCH₃, -OC(O)NH₂, -NHSO₂CH₃, and -OCF₃.

On Ring C preferred R⁵ substituents, when present, include -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, and -N(R⁴)SO₂R. More preferred R⁵ substituents include -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic). Examples of such preferred R⁵ substituents include -Cl, -F, -CN, -CF₃, -NH₂, -NHMe, -NMe₂, -OEt, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and -CO₂Et.

When G is Ring D, preferred formula V Ring D monocyclic rings include substituted and unsubstituted phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, and morpholinyl rings. When two adjacent substituents on Ring D are taken together to form a fused ring, the Ring D system is bicyclic. Preferred formula V Ring D bicyclic rings include 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, and

naphthyl. Examples of more preferred bicyclic Ring D systems include naphthyl and isoquinolinyl.

Preferred substituents on Ring D of formula V include one or more of the following: halo, oxo, CN, -NO₂, -N(R⁴)₂, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -SR, -OR, -C(O)R, or substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. More preferred Ring D substituents include -halo, -CN, -oxo, -SR, -OR, -N(R⁴)₂, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. Examples of Ring D substituents include -OH, phenyl, methyl, CH₂OH, CH₂CH₂OH, pyrrolidinyl, OPh, CF₃, C≡CH, Cl, Br, F, I, NH₂, C(O)CH₃, i-propyl, tert-butyl, SEt, OMe, N(Me)₂; methylene dioxy, and ethylene dioxy.

Preferred formula V compounds have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring,
20 optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring, and R¹ is -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶; or Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^x is hydrogen or C_{1-4} aliphatic and R^y is $T-R^3$, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted 5-7 membered unsaturated or partially unsaturated ring having 0-2 ring 5 nitrogens; and

(c) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C_{1-6} aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a 10 substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula V have one or more, and more preferably all, of the features selected from the group consisting of:

15 (a) Ring C is a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R^1 is -halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic 20 group, phenyl, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or 25 naphthyl;

(b) R^x is hydrogen or methyl and R^y is -R, $N(R^4)_2$, or -OR, or R^x and R^y are taken together with their intervening atoms to form a benzo ring or a 5-7 membered 30 partially unsaturated carbocyclo ring, said benzo or carbocyclo ring optionally substituted with -R, halo, -OR, $-C(=O)R$, $-CO_2R$, $-COCOR$, $-NO_2$, $-CN$, $-S(O)R$, $-SO_2R$, $-SR$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$,

-N(R⁴)CO₂ (optionally substituted C₁₋₆ aliphatic),

-N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂,

-N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

(c) R^{2'} is hydrogen and R² is hydrogen or a

5 substituted or unsubstituted group selected from aryl, or
a C₁₋₆ aliphatic group, or R² and R^{2'} are taken together
with their intervening atoms to form a substituted or
unsubstituted benzo, pyrido, pyrimido or partially
unsaturated 6-membered carbocyclo ring; and

10 (d) Ring D is substituted by oxo or R⁵, wherein
each R⁵ is independently selected from -halo, -CN, -NO₂,
-N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR,
-C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, or
-N(R⁴)SO₂R.

15 Even more preferred compounds of formula V have
one or more, and more preferably all, of the features
selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring,
optionally substituted by -R⁵, wherein when Ring C and two
20 adjacent substituents thereon form a bicyclic ring
system, the bicyclic ring system is a naphthyl ring, and
R¹ is -halo, a C₁₋₄ aliphatic group optionally substituted
with halogen, or -CN; or Ring D is an optionally
substituted ring selected from phenyl, pyridinyl,
25 piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl,
1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-
tetrahydroquinolinyl, isoquinolinyl, quinolinyl, or
naphthyl;

(b) R^x is hydrogen or methyl and R^y is methyl,
30 methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl,
alkyl- or an optionally substituted group selected from
2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^x and R^y
are taken together with their intervening atoms to form a

benzo ring or a 6-membered partially unsaturated carbocyclo ring optionally substituted with halo, CN, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, (C₁₋₆ alkyl)carbonyl, (C₁₋₆ alkyl)sulfonyl, mono- or dialkylamino, mono- or 5 dialkylaminocarbonyl, mono- or dialkylaminocarbonyloxy, or 5-6 membered heteroaryl;

(c) R² and R^{2'} are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring

10. optionally substituted with -halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, or -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group; and

(d) Ring D is substituted by oxo or R⁵, wherein each R⁵ is independently selected from -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic).

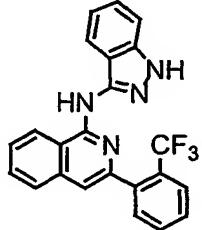
20 Representative compounds of formula V are set forth in Table 4 below.

Table 4.

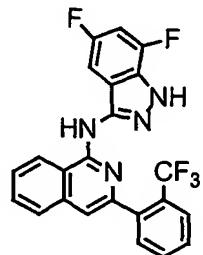
25



V-1



V-2



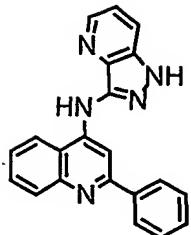
V-3



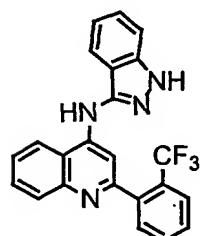
V-4



V-5

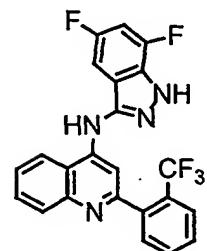


V-6

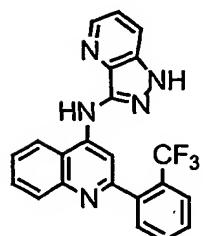


5

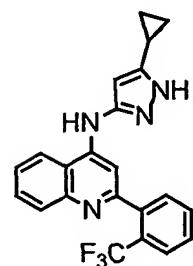
V-7



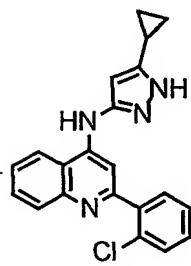
V-8



V-9



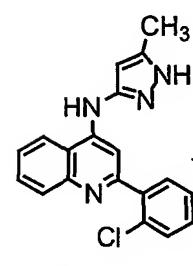
V-10



V-11

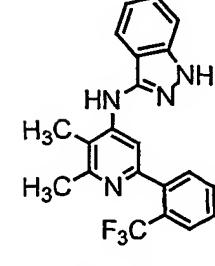


V-12

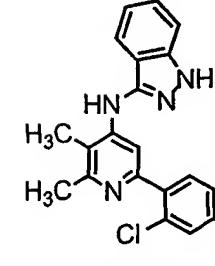


10

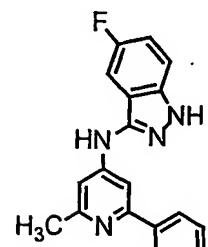
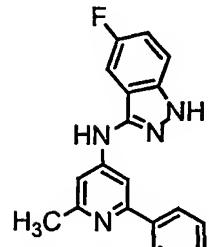
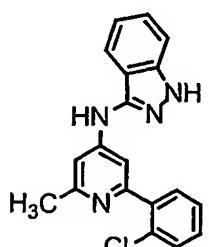
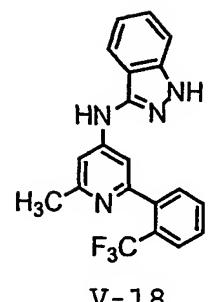
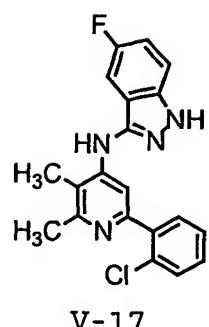
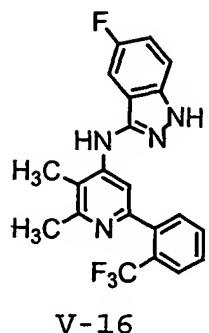
V-13



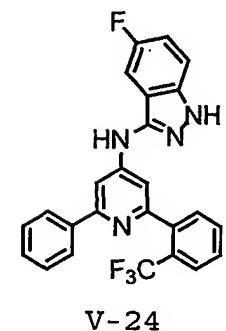
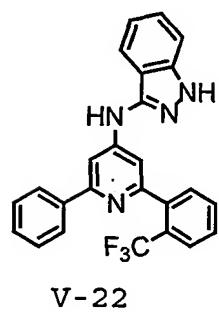
V-14



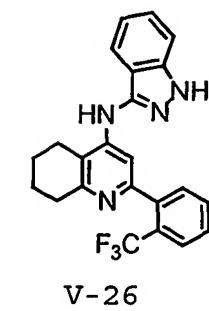
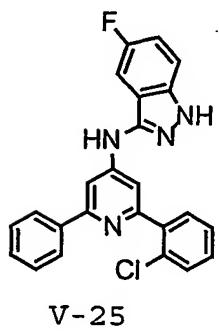
V-15



5



10

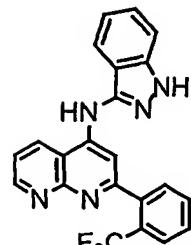




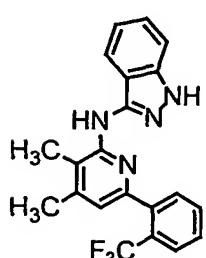
V-28



V-29

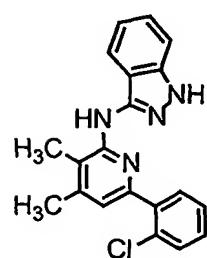


V-30

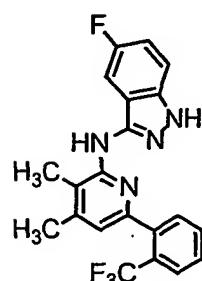


5

V-31



V-32



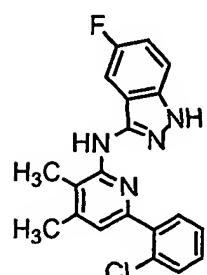
V-33



V-34



V-35



V-36

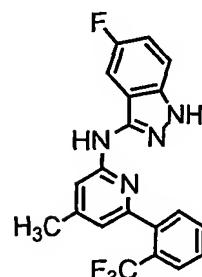


10

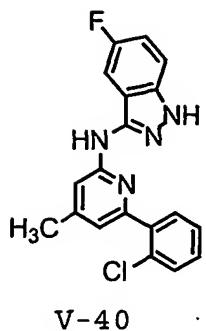
V-37



V-38



V-39



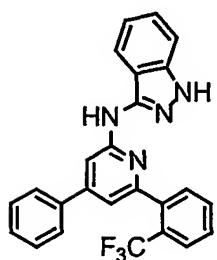
V-40



V-41

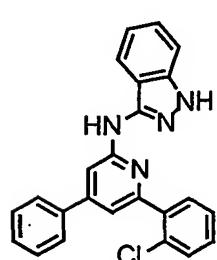


V-42

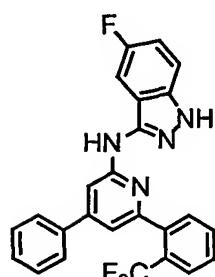


5

V-43



V-44



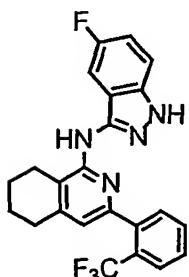
V-45



V-46



V-47



V-48



10

V-49



V-50



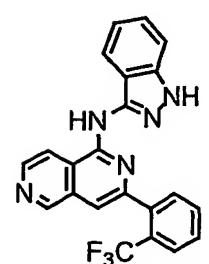
V-51



V-52



V-53

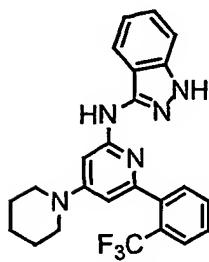


V-54

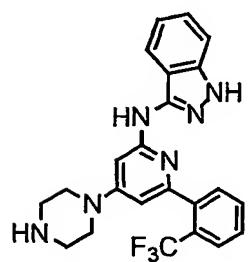


5

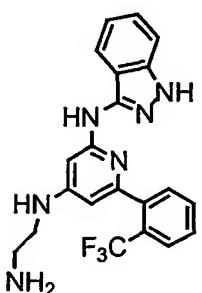
V-55



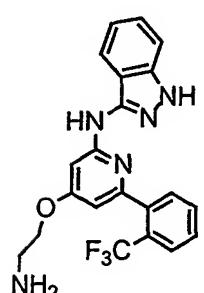
V-56



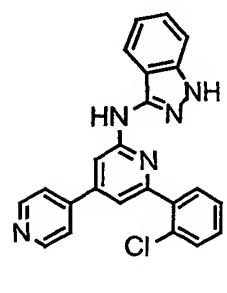
V-57



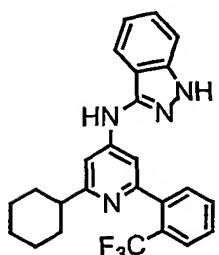
V-58



V-59

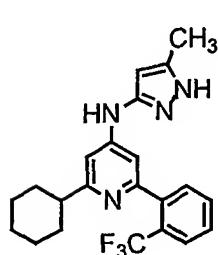


V-60

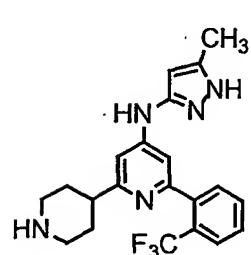


10

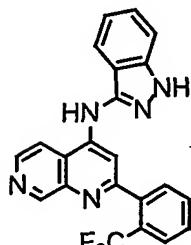
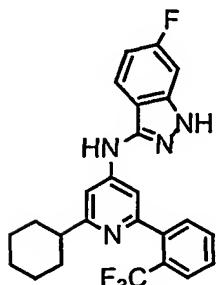
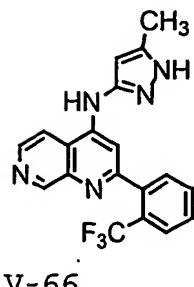
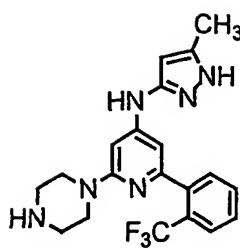
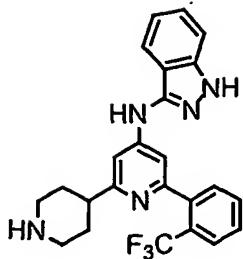
V-61



V-62



V-63



5

In another embodiment, this invention provides a composition comprising a compound of formula V and a pharmaceutically acceptable carrier.

10 One aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula V.

15 Another aspect relates to a method of treating a disease that is alleviated by treatment with a GSK-3 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula V.

20 Another aspect relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula

25

v. This method is especially useful for diabetic patients.

Another aspect relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula v. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

10 Another aspect relates to a method of inhibiting the phosphorylation of β -catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula V. This method is especially useful for treating schizophrenia.

15 One aspect of this invention relates to a method of inhibiting Aurora activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula V.

20 Another aspect relates to a method of treating a disease that is alleviated by treatment with an Aurora inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula V. This method is especially useful for treating cancer, such as colon, ovarian, and breast cancer.

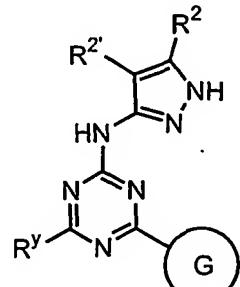
25 One aspect of this invention relates to a method of inhibiting CDK-2 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula V.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a CDK-2 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a 5 therapeutically effective amount of a composition comprising a compound of formula V. This method is especially useful for treating cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, 10 alopecia, and autoimmune diseases such as rheumatoid arthritis.

Another method relates to inhibiting GSK-3, Aurora, or CDK-2 activity in a biological sample, which method comprises contacting the biological sample with 15 the GSK-3 or Aurora inhibitor of formula V, or a pharmaceutical composition thereof, in an amount effective to inhibit GSK-3, Aurora or CDK-2.

Each of the aforementioned methods directed to the inhibition of GSK-3, Aurora or CDK-2, or the 20 treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula V, as described above.

Another embodiment of this invention relates to compounds of formula VI:



25

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C has one or two ortho substituents independently selected from -R¹, any substitutable non-ortho carbon position on Ring C is independently substituted by -R⁵, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or -R⁸;

10 Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or -R⁵, and at any substitutable ring nitrogen by -R⁴, provided that when Ring D is a six-membered aryl or heteroaryl ring, -R⁵ is hydrogen at each ortho carbon position of Ring D;

15 R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or -R⁸, said C₁₋₆ aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R¹

and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

R^Y is T-R^{3'};

T is a valence bond or a C₁₋₄ alkylidene chain;

R² and R^{2'} are independently selected from -R, -T-W-R⁶, or R² and R^{2'} are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R² and R^{2'} is substituted by halo, oxo, -CN, -NO₂, -R⁷, or -V-R⁶, and any substitutable nitrogen on said ring formed by R² and R^{2'} is substituted by R⁴;

5 R^{3'} is an optionally substituted group selected from C₁₋₆ aliphatic, C₃₋₁₀ carbocyclyl, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

15 each R⁵ is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, or R⁵ and

an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C; V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;

each R⁶ is independently selected from hydrogen, an optionally substituted C₁₋₄ aliphatic group, or two R⁶ groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

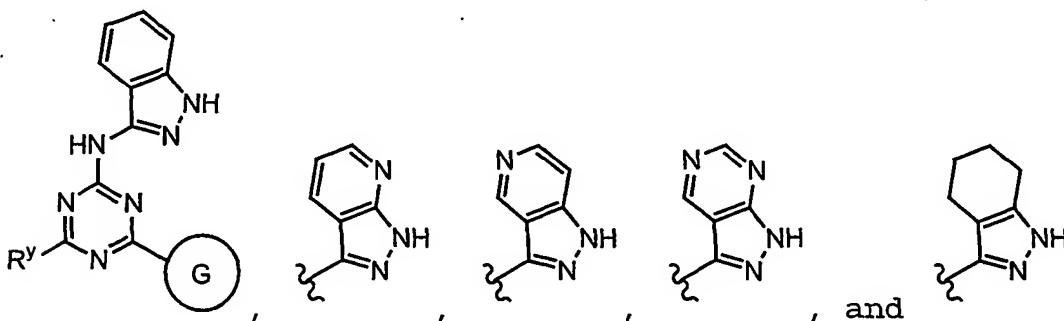
each R⁷ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R⁸ is independently selected from an optionally substituted C₁₋₄ aliphatic group, -OR⁶, -SR⁶, -COR⁶, -SO₂R⁶, -N(R⁶)₂, -N(R⁶)N(R⁶)₂, -CN, -NO₂, -CON(R⁶)₂, or -CO₂R⁶.

Preferred R^Y groups of formula VI include T-R^{3'} wherein T is a valence bond or a methylene, and R^{3'} is an optionally substituted group selected from C₁₋₆ aliphatic,

C_{3-10} carbocyclyl, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms. A preferred R^3' group is an optionally substituted group selected from C_{3-6} carbocyclyl, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring. Examples of preferred R^Y include 2-pyridyl, 4-pyridyl, piperidinyl, morpholinyl, cyclopropyl, cyclohexyl, and optionally substituted phenyl such as phenyl or halo-substituted phenyl.

The R^2 and R^2' groups of formula VI may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring. These are exemplified in the following formula VI compounds having a pyrazole-containing bicyclic ring system:



Preferred substituents on the R^2/R^2' fused ring include one or more of the following: -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4} \text{ alkyl})$, $-CO_2(C_{1-4} \text{ alkyl})$, $-CN$, $-SO_2(C_{1-4} \text{ alkyl})$, $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4} \text{ alkyl})$, $-NHC(O)(C_{1-4} \text{ alkyl})$, $-C(O)NH_2$, and $-CO(C_{1-4} \text{ alkyl})$, wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C_{1-4} alkyl) group is methyl.

When the pyrazole ring system is monocyclic, preferred R² groups of formula VI include hydrogen, C₁₋₄ aliphatic, alkoxy carbonyl, (un)substituted phenyl, hydroxy alkyl, alkoxy alkyl, aminocarbonyl, mono- or 5 dialkylaminocarbonyl, amino alkyl, alkylamino alkyl, dialkylamino alkyl, phenylaminocarbonyl, and (N-heterocyclyl)carbonyl. Examples of such preferred R² substituents include methyl, cyclopropyl, ethyl, isopropyl, propyl, t-butyl, cyclopentyl, phenyl, CO₂H, 10 CO₂CH₃, CH₂OH, CH₂OCH₃, CH₂CH₂CH₂OH, CH₂CH₂CH₂OCH₃, CH₂CH₂CH₂OCH₂Ph, CH₂CH₂CH₂NH₂, CH₂CH₂CH₂NHCOOC(CH₃)₃, CONHCH(CH₃)₂, CONHCH₂CH=CH₂, CONHCH₂CH₂OCH₃, CONHCH₂Ph, CONH(cyclohexyl), CON(Et)₂, CON(CH₃)CH₂Ph, CONH(n-C₃H₇), 15 CON(Et)CH₂CH₂CH₃, CONHCH₂CH(CH₃)₂, CON(n-C₃H₇)₂, CO(3-methoxymethylpyrrolidin-1-yl), CONH(3-tolyl), CONH(4-tolyl), CONHCH₃, CO(morpholin-1-yl), CO(4-methylpiperazin-1-yl), CONHCH₂CH₂OH, CONH₂, and CO(piperidin-1-yl). A preferred R²' group is hydrogen.

When G is Ring C, preferred formula VI Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring. Such rings preferably are fused at ortho and meta positions of Ring C. Examples of preferred bicyclic Ring C systems include naphthyl and isoquinolinyl. Preferred R¹ groups include -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶. 20 25 30 When R¹ is an optionally substituted C₁₋₆ aliphatic group, the most preferred optional substituents are halogen. Examples of preferred R¹ groups include -CF₃, -Cl, -F, -CN, -COCH₃, -OCH₃, -OH, -CH₂CH₃, -OCH₂CH₃, -CH₃, -CF₂CH₃,

cyclohexyl, t-butyl, isopropyl, cyclopropyl, -C≡CH, -C≡C-CH₃, -SO₂CH₃, -SO₂NH₂, -N(CH₃)₂, -CO₂CH₃, -CONH₂, -NHCOCH₃, -OC(O)NH₂, -NHSO₂CH₃, and -OCF₃.

On Ring C preferred R⁵ substituents, when present, include -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, and -N(R⁴)SO₂R. More preferred R⁵ substituents include -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic). Examples of such preferred R⁵ substituents include -Cl, -F, -CN, -CF₃, -NH₂, -NHMe, -NMe₂, -OEt, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and -CO₂Et.

When G is Ring D, preferred formula VI Ring D monocyclic rings include substituted and unsubstituted phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, and morpholinyl rings. When two adjacent substituents on Ring D are taken together to form a fused ring, the Ring D system is bicyclic. Preferred formula VI Ring D bicyclic rings include 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, and naphthyl. Examples of more preferred bicyclic Ring D systems include naphthyl and isoquinolinyl.

Preferred substituents on formula VI Ring D include one or more of the following: halo, oxo, CN, -NO₂, -N(R⁴)₂, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -SR, -OR, -C(O)R, or substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. More preferred Ring D substituents include -halo, -CN, -oxo, -SR, -OR, -N(R⁴)₂, -C(O)R, or a substituted or unsubstituted group selected from 5-6

membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. Examples of Ring D substituents include -OH, phenyl, methyl, CH₂OH, CH₂CH₂OH, pyrrolidinyl, OPh, CF₃, C≡CH, Cl, Br, F, I, NH₂, C(O)CH₃, *i*-propyl, *tert*-butyl, SEt, OMe, 5 N(Me)₂, methylene dioxy, and ethylene dioxy.

Preferred formula VI compounds have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is selected from a phenyl or 10 pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring, and R¹ is -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, 15 -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶; or Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 20 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^Y is T-R³', wherein T is a valence bond or a methylene; and

25 (c) R²' is hydrogen and R² is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C₁₋₆ aliphatic group, or R² and R²' are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or 30 partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula VI have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and 5 R¹ is -halo, a C₁₋₆ haloaliphatic group, a C₁₋₆ aliphatic group, phenyl, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-10 tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^Y is T-R^{3'}, wherein T is a valence bond or a methylene and R^{3'} is an optionally substituted group 15 selected from C₁₋₆ aliphatic, C₃₋₆ carbocyclyl, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

(c) R^{2'} is hydrogen and R² is hydrogen or a substituted or unsubstituted group selected from aryl, or 20 a C₁₋₆ aliphatic group, or R² and R^{2'} are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring; and

(d) Ring D is substituted by oxo or R⁵, wherein 25 each R⁵ is independently selected from -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, or -N(R⁴)SO₂R.

Even more preferred compounds of formula VI 30 have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R^Y is T-R^{3'}, wherein T is a valence bond or a methylene and R^{3'} is an optionally substituted group

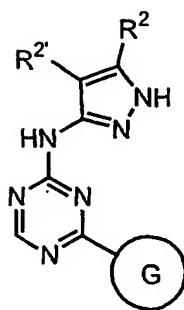
selected from C₁₋₄ aliphatic, C₃₋₆ carbocyclyl, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring;

(b) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R¹ is -halo, a C₁₋₄ aliphatic group optionally substituted with halogen, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, quinolinyl, or naphthyl;

(c) R² and R^{2'} are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, or -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group; and

(d) Ring D is substituted by oxo or R⁵, wherein each R⁵ is independently selected from -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic).

Another embodiment of this invention relates to compounds of formula VIIa:



VIIa

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl,

5 pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring,
wherein said Ring C has one or two ortho substituents
independently selected from -R¹, any substitutable non-
ortho carbon position on Ring C is independently
substituted by -R⁵, and two adjacent substituents on
10 Ring C are optionally taken together with their
intervening atoms to form a fused, unsaturated or
partially unsaturated, 5-6 membered ring having 0-3
heteroatoms selected from oxygen, sulfur or nitrogen,
said fused ring being optionally substituted by halo,
15 oxo, or -R⁸;

Ring D is a 5-7 membered monocyclic ring or 8-10 membered
bicyclic ring selected from aryl, heteroaryl,

20 heterocyclyl or carbocyclyl, said heteroaryl or
heterocyclyl ring having 1-4 ring heteroatoms selected
from nitrogen, oxygen or sulfur, wherein Ring D is
substituted at any substitutable ring carbon by oxo or
-R⁵, and at any substitutable ring nitrogen by -R⁴,
provided that when Ring D is a six-membered aryl or
heteroaryl ring, -R⁵ is hydrogen at each ortho carbon
25 position of Ring D;

R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or -R⁸, said C₁₋₆ aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R¹ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

5 T is a valence bond or a C₁₋₄ alkylidene chain;

10 R² and R^{2'} are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R²

15 and R^{2'} is substituted by halo, oxo, -CN, -NO₂, -R⁷, or -V-R⁶, and any substitutable nitrogen on said ring formed by R² and R^{2'} is substituted by R⁴;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

20 each R⁵ is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂,

25

-N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, or R⁵ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂- , -SO₂N(R⁶)-,

5 -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-,
 -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-,
 -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-,
 -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-,
 -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-,
 10 -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or
 -C(R⁶)₂N(R⁶)CON(R⁶)-;

W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-,
 -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-,
 -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-,
 15 -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-,
 -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-,
 -C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;

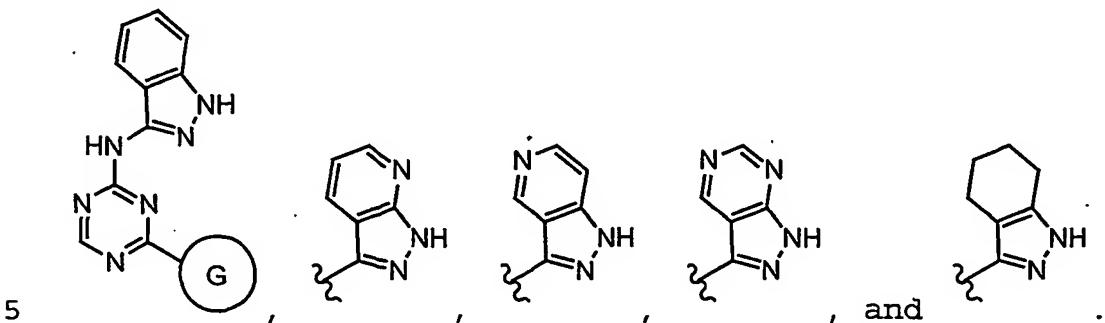
each R⁶ is independently selected from hydrogen, an optionally substituted C₁₋₄ aliphatic group, or two R⁶ groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

each R⁷ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R⁸ is independently selected from an optionally substituted C₁₋₄ aliphatic group, -OR⁶, -SR⁶, -COR⁶,
 30 -SO₂R⁶, -N(R⁶)₂, -N(R⁶)N(R⁶)₂, -CN, -NO₂, -CON(R⁶)₂, or -CO₂R⁶.

Preferred rings formed by the R² and R^{2'} groups of formula via include benzo, pyrido, pyrimido, and a

partially unsaturated 6-membered carbocyclo ring. These are exemplified in the following formula VIa compounds having a pyrazole-containing bicyclic ring system:



Preferred substituents on the R²/R^{2'} fused ring include one or more of the following: -halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, and -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C₁₋₄ alkyl) group is methyl.

When G is Ring C, preferred formula VIa Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring. Such rings preferably are fused at ortho and meta positions of Ring C. Examples of preferred bicyclic Ring C systems include naphthyl and isoquinolinyl. Preferred R¹ groups include -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶. When R¹ is an optionally substituted C₁₋₆ aliphatic group, the most preferred optional substituents are halogen. Examples of preferred R¹ groups include -CF₃, -Cl, -F,

-CN, -COCH₃, -OCH₃, -OH, -CH₂CH₃, -OCH₂CH₃, -CH₃, -CF₂CH₃, cyclohexyl, t-butyl, isopropyl, cyclopropyl, -C≡CH, -C≡C-CH₃, -SO₂CH₃, -SO₂NH₂, -N(CH₃)₂, -CO₂CH₃, -CONH₂, -NHCOCH₃, -OC(O)NH₂, -NHSO₂CH₃, and -OCF₃.

5 On Ring C preferred R⁵ substituents, when present, include -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, and -N(R⁴)SO₂R. More preferred R⁵ substituents include -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic). Examples of such preferred R⁵ substituents include -Cl, -F, -CN, -CF₃, -NH₂, -NHMe, -NMe₂, -OEt, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and -CO₂Et.

15 When G is Ring D, preferred formula VIa Ring D monocyclic rings include substituted and unsubstituted phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, and morpholinyl rings. When two adjacent substituents on Ring D are taken 20 together to form a fused ring, the Ring D system is bicyclic. Preferred formula VIa Ring D bicyclic rings include 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, and 25 naphthyl. Examples of more preferred bicyclic Ring D systems include naphthyl and isoquinolinyl.

Preferred substituents on the formula VIa Ring D include one or more of the following: halo, oxo, CN, -NO₂, -N(R⁴)₂, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -SR, -OR, -C(O)R, or substituted or 30 unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. More preferred Ring D substituents include -halo, -CN, -oxo, -SR, -OR,

-N(R⁴)₂, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. Examples of Ring D substituents include -OH, phenyl, methyl, CH₂OH, CH₂CH₂OH, pyrrolidinyl, OPh, CF₃, 5 C≡CH, Cl, Br, F, I, NH₂, C(O)CH₃, i-propyl, tert-butyl, SEt, OMe, N(Me)₂, methylene dioxy, and ethylene dioxy.

Preferred formula VIa compounds have one or more, and more preferably all, of the features selected from the group consisting of:

10 (a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring, and R¹ is 15 -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶; or Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, 20 thienyl, azepanyl, morpholiny, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring; and

25 (b) R² and R^{2'} are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula VIa have one or more, and more preferably all, of the features 30 selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring

system, the bicyclic ring system is a naphthyl ring, and R¹ is -halo, a C₁₋₆ haloaliphatic group, a C₁₋₆ aliphatic group, phenyl, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, 5 piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

10 (b) R² and R^{2'} are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, 15 -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, and -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group; and

20 (c) Ring D is substituted by oxo or R⁵, wherein each R⁵ is independently selected from -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, or -N(R⁴)SO₂R.

25 Even more preferred compounds of formula VIA have one or more, and more preferably all, of the features selected from the group consisting of:

30 (a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R¹ is -halo, a C₁₋₄ aliphatic group optionally substituted with halogen, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl,

piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, quinolinyl, or naphthyl;

5 (b) R² and R^{2'} are taken together with their intervening atoms to form a benzo, pyrido, or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, 10 -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, or -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group; and

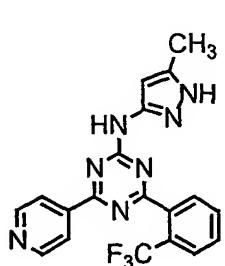
15 (d) Ring D is substituted by oxo or R⁵, wherein each R⁵ is independently selected from -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic).

Representative compounds of formula VI and IVa are set forth in Table 5 below.

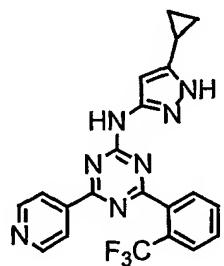
20

{

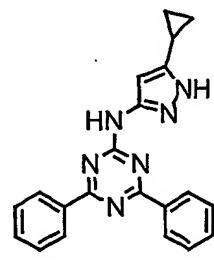
Table 5.



VI-1

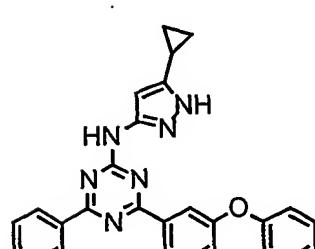
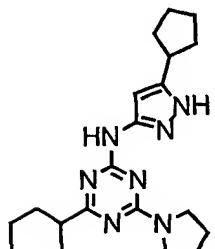
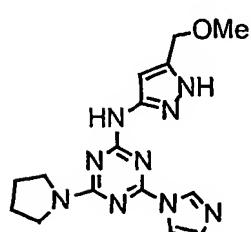
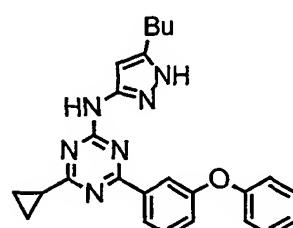
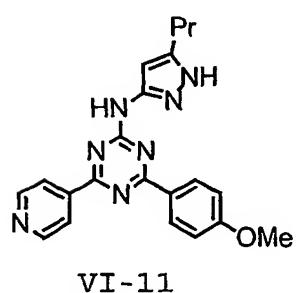
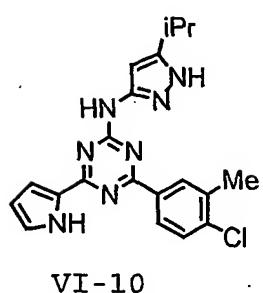
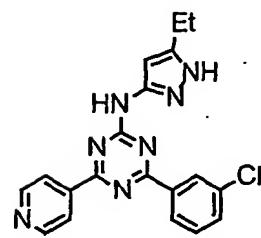
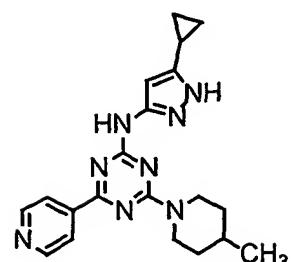
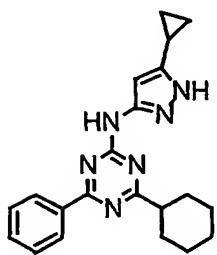
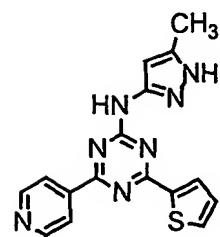
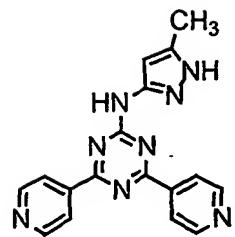
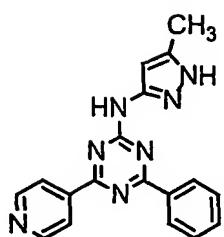


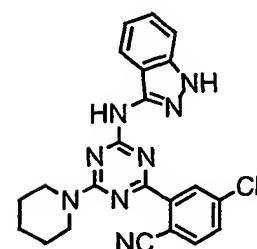
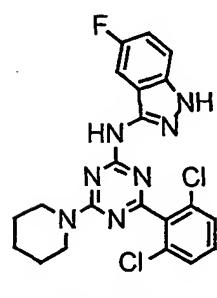
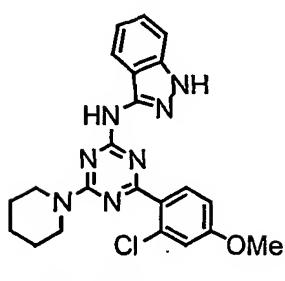
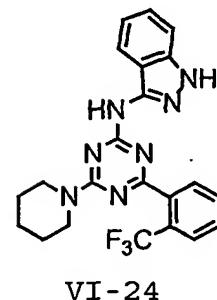
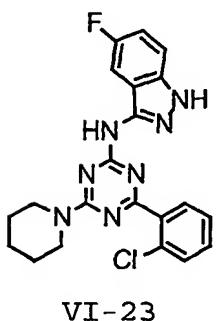
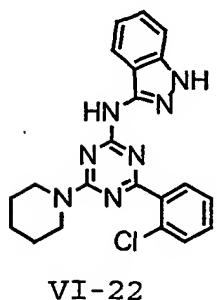
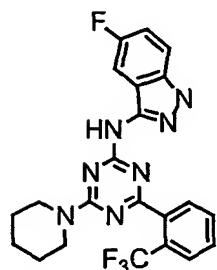
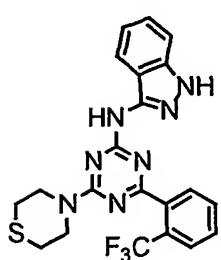
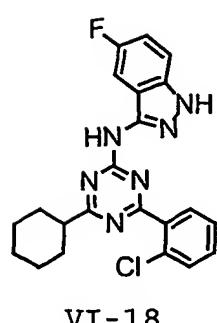
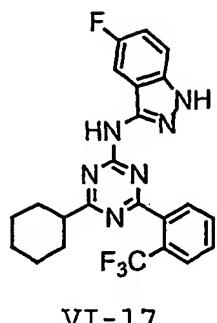
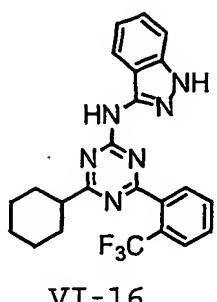
VI-2

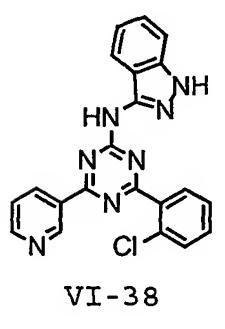
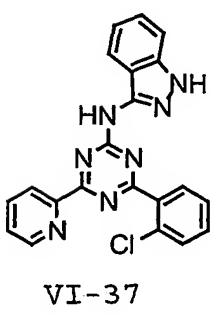
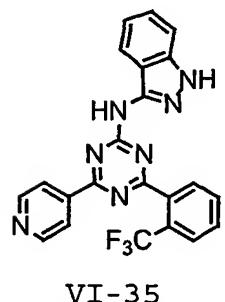
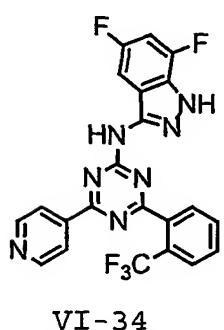
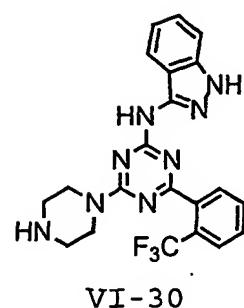
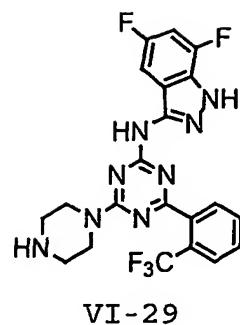
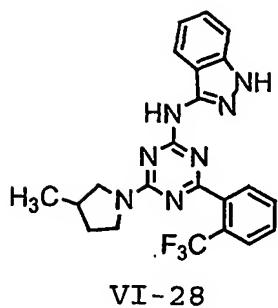


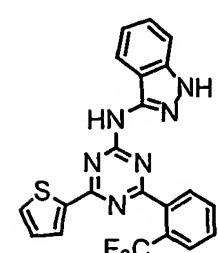
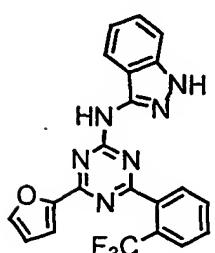
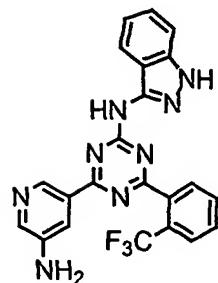
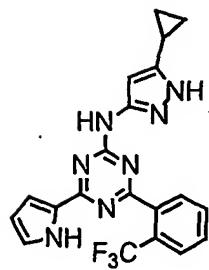
VI-3

25

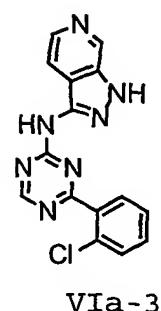
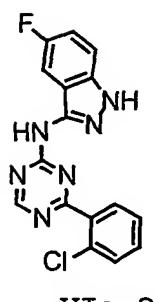
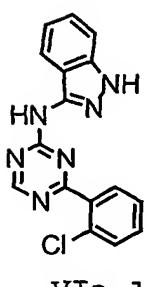




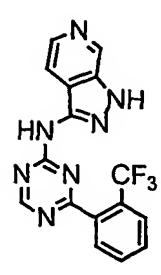
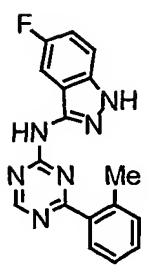


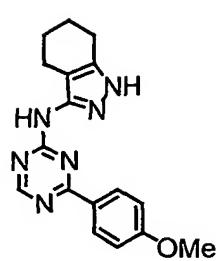
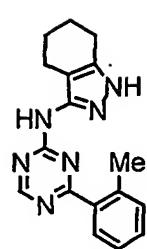


5



10





In another embodiment, this invention provides a composition comprising a compound of formula VI or VII and a pharmaceutically acceptable carrier.

One aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula VI or VII.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a GSK-3 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula VI or VII.

Another aspect relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising

administering to said patient a therapeutically effective amount of a composition comprising a compound of formula VI or VIIa. This method is especially useful for diabetic patients.

5 Another aspect relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula 10 VI or VIIa. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

Another aspect relates to a method of inhibiting the phosphorylation of β-catenin in a patient in need thereof, comprising administering to said patient 15 a therapeutically effective amount of a composition comprising a compound of formula VI or VIIa. This method is especially useful for treating schizophrenia.

One aspect of this invention relates to a method of inhibiting Aurora activity in a patient, 20 comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula VI or VIIa.

Another aspect relates to a method of treating a disease that is alleviated by treatment with an Aurora 25 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula VI or VIIa. This method is especially useful for treating cancer, such as colon, 30 ovarian, and breast cancer.

One aspect of this invention relates to a method of inhibiting CDK-2 activity in a patient, comprising administering to the patient a therapeutically

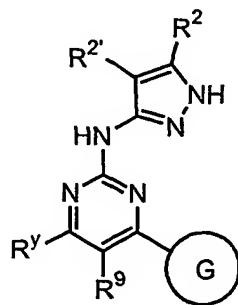
effective amount of a composition comprising a compound of formula VI or VIa.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a CDK-2 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula VI or VIa. This method is especially useful for treating cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid arthritis.

Another method relates to inhibiting GSK-3, Aurora, or CDK-2 activity in a biological sample, which method comprises contacting the biological sample with the GSK-3 or Aurora inhibitor of formula VI or VIa, or a pharmaceutical composition thereof, in an amount effective to inhibit GSK-3, Aurora or CDK-2.

Each of the aforementioned methods directed to the inhibition of GSK-3, Aurora or CDK-2, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula VI or VIa, as described above.

Another embodiment of this invention relates to compounds of formula VII:



VII

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring,

5 wherein said Ring C has one or two ortho substituents independently selected from -R¹, any substitutable non-ortho carbon position on Ring C is independently substituted by -R⁵, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or -R⁸;

10 15 Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or -R⁵, and at any substitutable ring nitrogen by -R⁴, provided that when Ring D is a six-membered aryl or heteroaryl ring, -R⁵ is hydrogen at each ortho carbon position of Ring D;

20 25 R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or -R⁸, said C₁₋₆ aliphatic group optionally

substituted with halo, cyano, nitro, or oxygen, or R¹ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

R^y is hydrogen or T-R^{3"};

T is a valence bond, hydrogen, or a C₁₋₄ alkylidene chain;

R² and R^{2'} are independently selected from -R, -T-W-R⁶, or

5 R² and R^{2'} are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R² and R^{2'} is substituted by halo, oxo, -CN, -NO₂, -R⁷, or -V-R⁶, and any substitutable nitrogen on said ring formed by R² and R^{2'} is substituted by R⁴;

10 R^{3"} is selected from an optionally substituted group selected from C₃₋₁₀ carbocyclyl, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂,

15 or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R⁵ is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR,

20 -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂,

-N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, or R⁵ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-,

5 -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-,

10 -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-,

15 -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;

each R⁶ is independently selected from hydrogen, an optionally substituted C₁₋₄ aliphatic group, or two R⁶ groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

each R⁷ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring;

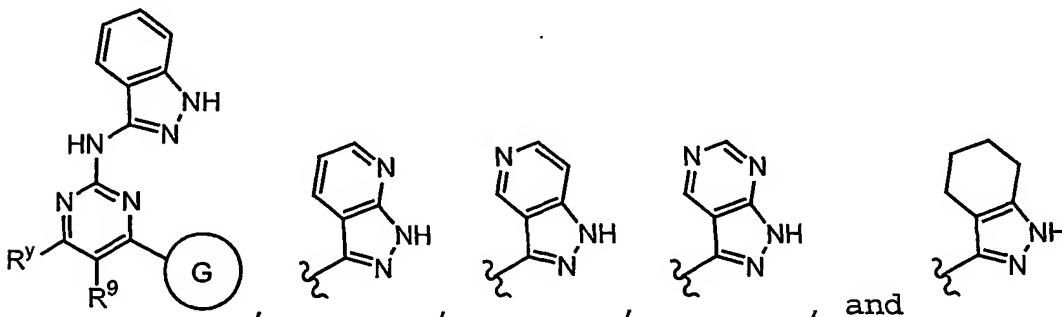
each R⁸ is independently selected from an optionally substituted C₁₋₄ aliphatic group, -OR⁶, -SR⁶, -COR⁶, -SO₂R⁶, -N(R⁶)₂, -N(R⁶)N(R⁶)₂, -CN, -NO₂, -CON(R⁶)₂, or -CO₂R⁶; and

R⁹ is selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂,

$-\text{SO}_2\text{N}(\text{R}^4)_2$, $-\text{OC}(=\text{O})\text{R}$, $-\text{N}(\text{R}^4)\text{COR}$, $-\text{N}(\text{R}^4)\text{CO}_2$ (optionally substituted C_{1-6} aliphatic), $-\text{N}(\text{R}^4)\text{N}(\text{R}^4)_2$, $-\text{C}=\text{NN}(\text{R}^4)_2$, $-\text{C}=\text{N}-\text{OR}$, $-\text{N}(\text{R}^4)\text{CON}(\text{R}^4)_2$, $-\text{N}(\text{R}^4)\text{SO}_2\text{N}(\text{R}^4)_2$, $-\text{N}(\text{R}^4)\text{SO}_2\text{R}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^4)_2$.

5 Preferred R^y groups of formula VII include $\text{T}-\text{R}^{3''}$ wherein T is a valence bond or a methylene. Preferred $\text{R}^{3''}$ groups include an optionally substituted group selected from C_{3-6} carbocyclyl, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring. Examples of preferred R^y 10 include 2-pyridyl, 4-pyridyl, piperidinyl, cyclopropyl, and an optionally substituted phenyl such as phenyl or halo-substituted phenyl.

The R^2 and $\text{R}^{2'}$ groups of formula VII may be taken together to form a fused ring, thus providing a 15 bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring. These are exemplified in the following formula VII compounds having a pyrazole-containing bicyclic ring 20 system:



Preferred substituents on the $\text{R}^2/\text{R}^{2'}$ fused ring 25 include one or more of the following: -halo, $-\text{N}(\text{R}^4)_2$, $-\text{C}_{1-4}$ alkyl, $-\text{C}_{1-4}$ haloalkyl, $-\text{NO}_2$, $-\text{O}(\text{C}_{1-4}\text{ alkyl})$, $-\text{CO}_2(\text{C}_{1-4}$ alkyl), $-\text{CN}$, $-\text{SO}_2(\text{C}_{1-4}\text{ alkyl})$, $-\text{SO}_2\text{NH}_2$, $-\text{OC}(\text{O})\text{NH}_2$, $-\text{NH}_2\text{SO}_2(\text{C}_{1-4}\text{ alkyl})$, $-\text{NHC}(\text{O})(\text{C}_{1-4}\text{ alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, and

-CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C₁₋₄ alkyl) group is methyl.

When the pyrazole ring system of formula VII is monocyclic, preferred R² groups include hydrogen, C₁₋₄ aliphatic, alkoxycarbonyl, (un)substituted phenyl, hydroxyalkyl, alkoxyalkyl, aminocarbonyl, mono- or dialkylaminocarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonyl, and (N-heterocyclyl)carbonyl. Examples of such preferred R² substituents include methyl, cyclopropyl, ethyl, isopropyl, propyl, t-butyl, cyclopentyl, phenyl, CO₂H, CO₂CH₃, CH₂OH, CH₂OCH₃, CH₂CH₂CH₂OH, CH₂CH₂CH₂OCH₃, CH₂CH₂CH₂OCH₂Ph, CH₂CH₂CH₂NH₂, CH₂CH₂CH₂NHCOOC(CH₃)₃, CONHCH(CH₃)₂, CONHCH₂CH=CH₂, CONHCH₂CH₂OCH₃, CONHCH₂Ph, CONH(cyclohexyl), CON(Et)₂, CON(CH₃)CH₂Ph, CONH(n-C₃H₇), CON(Et)CH₂CH₂CH₃, CONHCH₂CH(CH₃)₂, CON(n-C₃H₇)₂, CO(3-methoxymethylpyrrolidin-1-yl), CONH(3-tolyl), CONH(4-tolyl), CONHCH₃, CO(morpholin-1-yl), CO(4-methylpiperazin-1-yl), CONHCH₂CH₂OH, CONH₂, and CO(piperidin-1-yl). A preferred R² group is hydrogen.

When G is Ring C, preferred formula VII Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring. Such rings preferably are fused at ortho and meta positions of Ring C. Examples of preferred bicyclic Ring C systems include naphthyl and isoquinolinyl. Preferred R¹ groups include -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶. When R¹ is an optionally substituted C₁₋₆ aliphatic group,

the most preferred optional substituents are halogen. Examples of preferred R¹ groups include -CF₃, -Cl, -F, -CN, -COCH₃, -OCH₃, -OH, -CH₂CH₃, -OCH₂CH₃, -CH₃, -CF₂CH₃, cyclohexyl, t-butyl, isopropyl, cyclopropyl, -C≡CH, 5 -C≡C-CH₃, -SO₂CH₃, -SO₂NH₂, -N(CH₃)₂, -CO₂CH₃, -CONH₂, -NHCOCH₃, -OC(O)NH₂, -NHSO₂CH₃, and -OCF₃.

On Ring C preferred R⁵ substituents, when present, include -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, 10 -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, and -N(R⁴)SO₂R. More preferred R⁵ substituents include -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic). Examples of such preferred R⁵ substituents include -Cl, 15 -F, -CN, -CF₃, -NH₂, -NHMe, -NMe₂, -OEt, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and -CO₂Et.

When G is Ring D, preferred formula VII Ring D monocyclic rings include substituted and unsubstituted phenyl, pyridinyl, piperidinyl, piperazinyl, 20 pyrrolidinyl, thienyl, azepanyl, and morpholinyl rings. When two adjacent substituents on Ring D are taken together to form a fused ring, the Ring D system is bicyclic. Preferred formula VII Ring D bicyclic rings include 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, and naphthyl. Examples of more preferred bicyclic Ring D systems include naphthyl and isoquinolinyl.

Preferred substituents on Ring D include one or 30 more of the following: halo, oxo, CN, -NO₂, -N(R⁴)₂, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -SR, -OR, -C(O)R, or substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆

aliphatic. More preferred Ring D substituents include -halo, -CN, -oxo, -SR, -OR, -N(R⁴)₂, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic.

5 Examples of Ring D substituents include -OH, phenyl, methyl, CH₂OH, CH₂CH₂OH, pyrrolidinyl, OPh, CF₃, C≡CH, Cl, Br, F, I, NH₂, C(O)CH₃, i-propyl, tert-butyl, SEt, OMe, N(Me)₂, methylene dioxy, and ethylene dioxy.

Preferred formula VII compounds have one or
10 more, and more preferably all, of the features selected
from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring,
optionally substituted by -R⁵, wherein when Ring C and two
adjacent substituents thereon form a bicyclic ring
15 system, the bicyclic ring system is selected from a
naphthyl, quinolinyl or isoquinolinyl ring, and R¹ is
-halo, an optionally substituted C₁₋₆ aliphatic group,
phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶,
-CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶; or Ring D is an
20 optionally substituted ring selected from a phenyl,
pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl,
thienyl, azepanyl, morpholinyl, 1,2,3,4-
tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl,
2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl,
25 isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^Y is T-R³", wherein T is a valence bond or
a methylene; and

(c) R^{2'} is hydrogen and R² is hydrogen or a
substituted or unsubstituted group selected from aryl,
30 heteroaryl, or a C₁₋₆ aliphatic group, or R² and R^{2'} are
taken together with their intervening atoms to form a
substituted or unsubstituted benzo, pyrido, pyrimido or
partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula VII have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring,
5 optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R¹ is -halo, a C₁₋₆ haloaliphatic group, a C₁₋₆ aliphatic group, phenyl, or -CN; or Ring D is an optionally
10 substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or
15 naphthyl;

(b) R^Y is T-R^{3"}, wherein T is a valence bond or a methylene and R^{3"} is an optionally substituted group selected from C₃₋₆ carbocyclyl, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring;

20 (c) R^{2'} is hydrogen and R² is hydrogen or a substituted or unsubstituted group selected from aryl, or a C₁₋₆ aliphatic group, or R² and R^{2'} are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially
25 unsaturated 6-membered carbocyclo ring; and

(d) Ring D is substituted by oxo or R⁵, wherein each R⁵ is independently selected from -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, or
30 -N(R⁴)SO₂R.

Even more preferred compounds of formula VII have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R^Y is $T-R^{3''}$, wherein T is a valence bond or a methylene and $R^{3''}$ is an optionally substituted group selected from phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring;

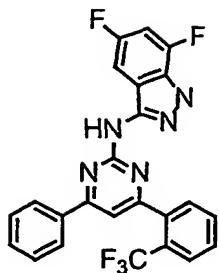
5 (b) Ring C is a phenyl or pyridinyl ring, optionally substituted by $-R^5$, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R^1 is -halo, a C_{1-4} aliphatic group optionally substituted
10 with halogen, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, quinolinyl, or
15 naphthyl;

(c) R^2 and $R^{2'}$ are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4} \text{ alkyl})$, $-CO_2(C_{1-4} \text{ alkyl})$, -CN, $-SO_2(C_{1-4} \text{ alkyl})$, $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4} \text{ alkyl})$, $-NHC(O)(C_{1-4} \text{ alkyl})$, $-C(O)NH_2$, or $-CO(C_{1-4} \text{ alkyl})$, wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group; and

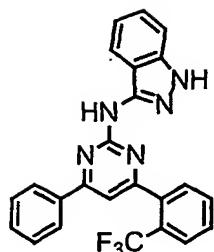
25 (d) Ring D is substituted by oxo or R^5 , wherein each R^5 is independently selected from -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4} \text{ aliphatic})$, $-N(C_{1-4} \text{ aliphatic})_2$, $-O(C_{1-4} \text{ aliphatic})$, C_{1-4} aliphatic, and $-CO_2(C_{1-4} \text{ aliphatic})$.

Representative compounds of formula VII are set forth in Table 6 below.

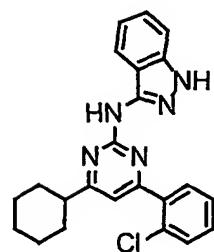
Table 6.



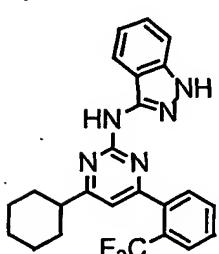
VII-1



VII-2

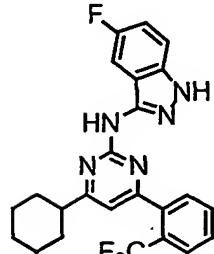


VII-3

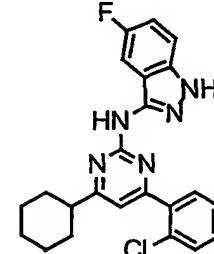


5

VII-4



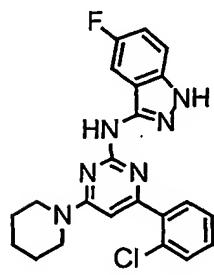
VII-5



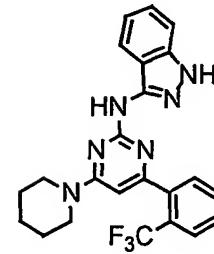
VII-6



VII-7



VII-8

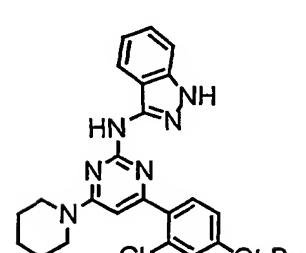


VII-9

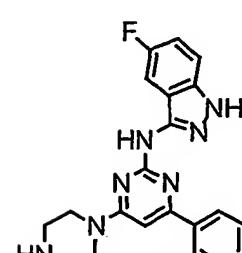


10

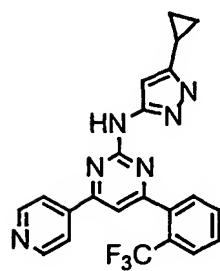
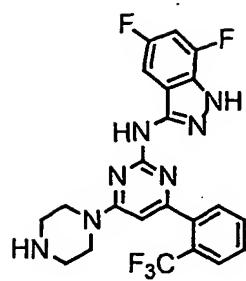
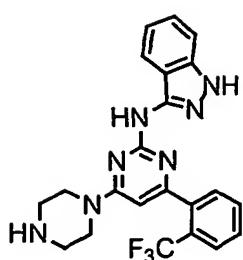
VII-10



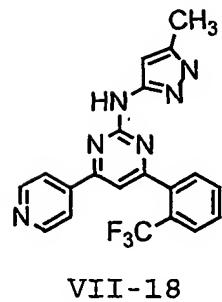
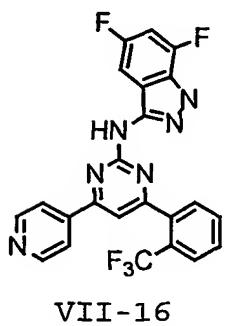
VII-11



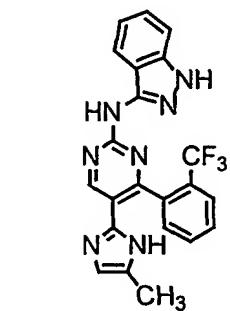
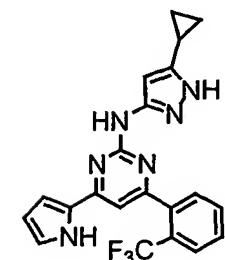
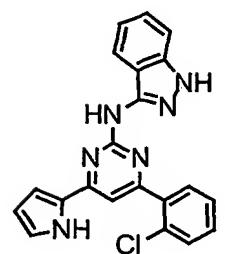
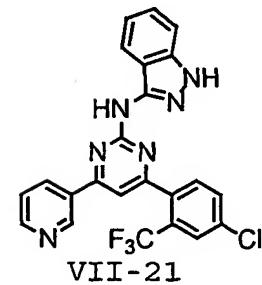
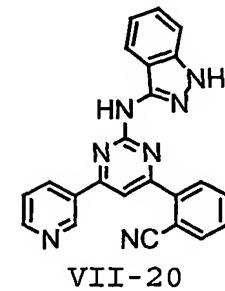
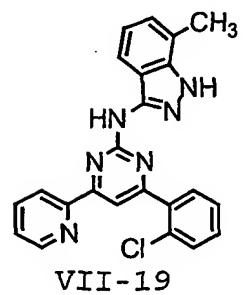
VII-12

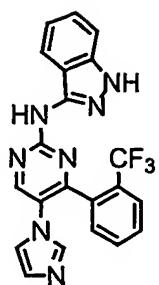


5

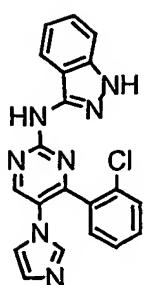


10

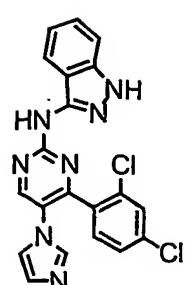




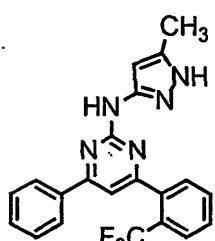
VII-25



VII-26

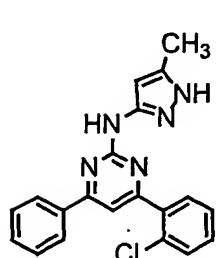


VII-27

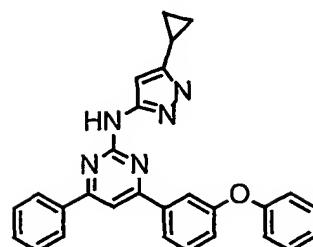


5

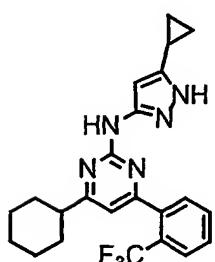
VII-28



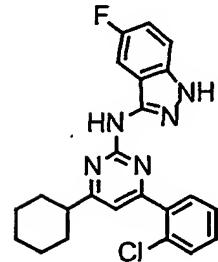
VII-29



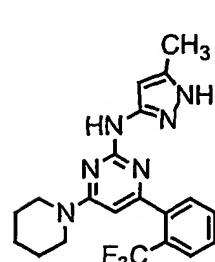
VII-30



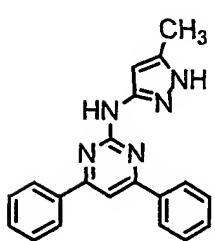
VII-31



VII-32

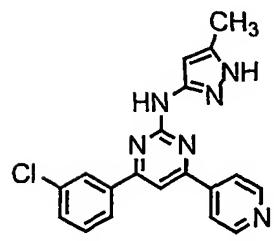


VII-33

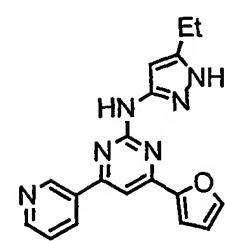


10

VII-34



VII-35



VII-36

In another embodiment, this invention provides a composition comprising a compound of formula VII and a pharmaceutically acceptable carrier.

One aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound 5 of formula VII.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a GSK-3 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a 10 therapeutically effective amount of a composition comprising a compound of formula VII.

Another aspect relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising 15 administering to said patient a therapeutically effective amount of a composition comprising a compound of formula VII. This method is especially useful for diabetic patients.

Another aspect relates to a method of 20 inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula VII. This method is especially useful in halting or 25 slowing the progression of Alzheimer's disease.

Another aspect relates to a method of inhibiting the phosphorylation of β -catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition 30 comprising a compound of formula VII. This method is especially useful for treating schizophrenia.

One aspect of this invention relates to a method of inhibiting Aurora activity in a patient,

comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula VII.

Another aspect relates to a method of treating
5 a disease that is alleviated by treatment with an Aurora inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula VII. This method is
10 especially useful for treating cancer, such as colon, ovarian, and breast cancer.

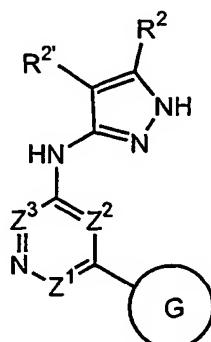
One aspect of this invention relates to a method of inhibiting CDK-2 activity in a patient, comprising administering to the patient a therapeutically
15 effective amount of a composition comprising a compound of formula VII.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a CDK-2 inhibitor, said method comprising the step of
20 administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula VII. This method is especially useful for treating cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis,
25 cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid arthritis.

Another method relates to inhibiting GSK-3, Aurora, or CDK-2 activity in a biological sample, which
30 method comprises contacting the biological sample with the GSK-3 or Aurora inhibitor of formula VII, or a pharmaceutical composition thereof, in an amount effective to inhibit GSK-3, Aurora or CDK-2.

Each of the aforementioned methods directed to the inhibition of GSK-3, Aurora or CDK-2, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula VII, as 5 described above.

Another embodiment of this invention relates to compounds of formula VIII:



10

VIII

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

Z^1 is N or CR⁹, Z^2 is N or CH, and Z^3 is N or CR^x, provided that one of Z^1 and Z^3 is nitrogen;

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring,

15 wherein said Ring C has one or two ortho substituents independently selected from -R¹, any substitutable non-ortho carbon position on Ring C is independently substituted by -R⁵, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen,

20 said fused ring being optionally substituted by halo, oxo, or -R⁸;

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by halo, oxo, or -R⁵, and at any substitutable ring nitrogen by -R⁴, provided that when Ring D is a six-membered aryl or heteroaryl ring, -R⁵ is hydrogen at each ortho carbon position of Ring D;

R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or -R⁸, said C₁₋₆ aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R¹ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

R^x is T-R³;

T is a valence bond or a C₁₋₄ alkylidene chain;

R² and R^{2'} are independently selected from -R, -T-W-R⁶, or R² and R^{2'} are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R² and R^{2'} is substituted by halo, oxo, -CN, -NO₂, -R⁷, or -V-R⁶, and any substitutable nitrogen on said ring formed by R² and R^{2'} is substituted by R⁴;

R³ is selected from -R, -halo, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR,

-N(R⁷)CO₂ (optionally substituted C₁₋₆ aliphatic),
 -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂,
 -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁷)₂;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂ (optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or

5 heteroaryl ring;

each R⁵ is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂ (optionally substituted C₁₋₆ aliphatic),

10 -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, or R⁵ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-,

15 -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, 20 -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-,

-C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-, 25 -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-,

$-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$,

$-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;

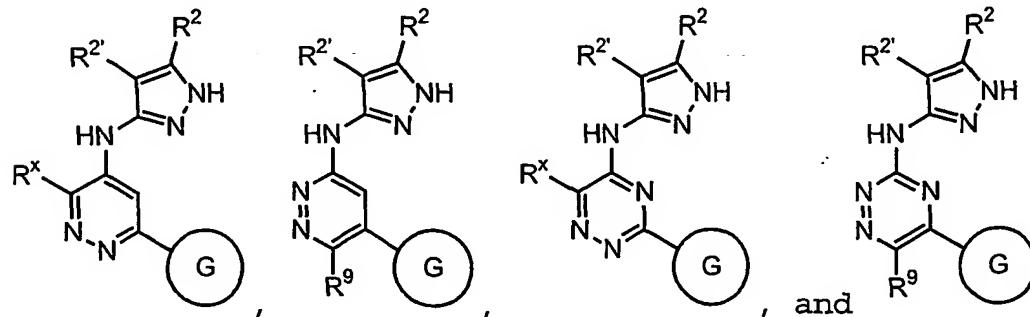
each R^6 is independently selected from hydrogen, an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^8 is independently selected from an optionally substituted C_{1-4} aliphatic group, $-OR^6$, $-SR^6$, $-COR^6$, $-SO_2R^6$, $-N(R^6)_2$, $-N(R^6)N(R^6)_2$, $-CN$, $-NO_2$, $-CON(R^6)_2$, or $-CO_2R^6$; and

R^9 is selected from $-R$, halo, $-OR$, $-C(=O)R$, $-CO_2R$, $-COCOR$, $-NO_2$, $-CN$, $-S(O)R$, $-SO_2R$, $-SR$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$ (optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$.

Accordingly, the present invention relates to compounds of formula VIIIA, VIIIB, VIIIC and VIIID as shown below:



VIIIfa

VIIIfb

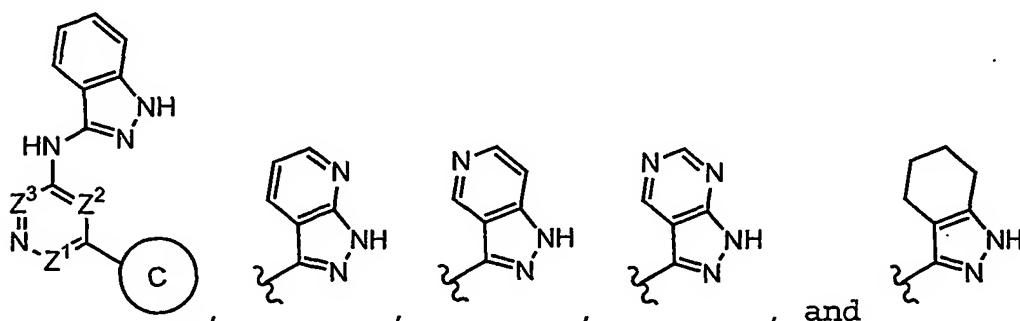
VIIIfc

VIIIfd

Preferred R^x groups of formula VIII include T-R³ wherein T is a valence bond or a methylene and R³ is CN, -R, or -OR. When R³ is -R, preferred R³ groups include an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring. When R³ is -OR, preferred R groups include an optionally substituted group C₁₋₆ aliphatic group such as alkyl- or dialkylaminoalkyl and aminoalkyl. Examples of preferred R^x include acetamido, CN, piperidinyl, piperazinyl, phenyl, pyridinyl, imidazol-1-yl, imidazol-2-yl, cyclohexyl, cyclopropyl, methyl, ethyl, isopropyl, t-butyl, NH₂CH₂CH₂NH, and NH₂CH₂CH₂O.

Preferred R⁹ groups of formula VIII, when present, include R, OR, and N(R⁴)₂. Examples of preferred R⁹ include methyl, ethyl, NH₂, NH₂CH₂CH₂NH, N(CH₃)₂CH₂CH₂NH, N(CH₃)₂CH₂CH₂O, (piperidin-1-yl)CH₂CH₂O, and NH₂CH₂CH₂O.

The R² and R^{2'} groups of formula VIII may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocyclo ring. These are exemplified in the following formula VIII compounds having a pyrazole-containing bicyclic ring system:



Preferred substituents on the formula VIII

R²/R^{2'} fused ring include one or more of the following:

-halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, and -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C₁₋₄ alkyl) group is methyl.

When the pyrazole ring system of formula VIII is monocyclic, preferred R² groups include hydrogen, C₁₋₄ aliphatic, alkoxycarbonyl, (un)substituted phenyl, hydroxyalkyl, alkoxyalkyl, aminocarbonyl, mono- or dialkylaminocarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonyl, and (N-heterocycl)carbonyl. Examples of such preferred R² substituents include methyl, cyclopropyl, ethyl, isopropyl, propyl, t-butyl, cyclopentyl, phenyl, CO₂H, CO₂CH₃, CH₂OH, CH₂OCH₃, CH₂CH₂CH₂OH, CH₂CH₂CH₂OCH₃, CH₂CH₂CH₂OCH₂Ph, CH₂CH₂CH₂NH₂, CH₂CH₂CH₂NHCOOC(CH₃)₃, CONHCH(CH₃)₂, CONHCH₂CH=CH₂, CONHCH₂CH₂OCH₃, CONHCH₂Ph, CONH(cyclohexyl), CON(Et)₂, CON(CH₃)CH₂Ph, CONH(n-C₃H₇), CON(Et)CH₂CH₂CH₃, CONHCH₂CH(CH₃)₂, CON(n-C₃H₇)₂, CO(3-methoxymethylpyrrolidin-1-yl), CONH(3-tolyl), CONH(4-tolyl), CONHCH₃, CO(morpholin-1-yl), CO(4-methylpiperazin-1-yl), CONHCH₂CH₂OH, CONH₂, and CO(piperidin-1-yl). A preferred R^{2'} group is hydrogen.

When G is Ring C, preferred formula VIII Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring. Such rings preferably are fused at ortho and meta

positions of Ring C. Examples of preferred bicyclic Ring C systems include naphthyl and isoquinolinyl. Preferred R¹ groups include -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, 5 -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶. When R¹ is an optionally substituted C₁₋₆ aliphatic group, the most preferred optional substituents are halogen. Examples of preferred R¹ groups include -CF₃, -Cl, -F, 10 -CN, -COCH₃, -OCH₃, -OH, -CH₂CH₃, -OCH₂CH₃, -CH₃, -CF₂CH₃, cyclohexyl, t-butyl, isopropyl, cyclopropyl, -C≡CH, -C≡C-CH₃, -SO₂CH₃, -SO₂NH₂, -N(CH₃)₂, -CO₂CH₃, -CONH₂, -NHCOCH₃, -OC(O)NH₂, -NHSO₂CH₃, and -OCF₃.

On Ring C preferred R⁵ substituents, when present, include -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, 15 -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, and -N(R⁴)SO₂R. More preferred R⁵ substituents include -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic). 20 Examples of such preferred R⁵ substituents include -Cl, -F, -CN, -CF₃, -NH₂, -NHMe, -NMe₂, -OEt, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and -CO₂Et.

When G is Ring D, preferred formula VIII Ring D monocyclic rings include substituted and unsubstituted 25 phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, and morpholinyl rings. When two adjacent substituents on Ring D are taken together to form a fused ring, the Ring D system is bicyclic. Preferred formula VIII Ring D bicyclic rings 30 include 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, and

naphthyl. Examples of more preferred bicyclic Ring D systems include naphthyl and isoquinolinyl.

Preferred R⁵ substituents on Ring D of formula VIII include halo, oxo, CN, -NO₂, -N(R⁴)₂, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -SR, -OR, -C(O)R, or substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. More preferred R⁵ substituents include -halo, -CN, -oxo, -SR, -OR, -N(R⁴)₂, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic. Examples of Ring D substituents include -OH, phenyl, methyl, CH₂OH, CH₂CH₂OH, pyrrolidinyl, OPh, CF₃, C≡CH, Cl, Br, F, I, NH₂, C(O)CH₃, *i*-propyl, *tert*-butyl, SEt, OMe, N(Me)₂, methylene dioxy, and ethylene dioxy.

Preferred formula VIII compounds have one or more, and more preferably all, of the features selected from the group consisting of:

- (a) Ring C is a phenyl or pyridinyl ring,
20 optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring, and R¹ is -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶; or Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^x is $T-R^3$ wherein T is a valence bond or a methylene; and

(c) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, 5 heteroaryl, or a C₁₋₆ aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

More preferred compounds of formula VIII have 10 one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by - R^5 , wherein when Ring C and two adjacent substituents thereon form a bicyclic ring 15 system, the bicyclic ring system is a naphthyl ring, and R^1 is -halo, a C₁₋₆ haloaliphatic group, a C₁₋₆ aliphatic group, phenyl, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 20 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^x is $T-R^3$ wherein T is a valence bond or a 25 methylene and R^3 is CN, -R or -OR;

(c) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, or a C₁₋₆ aliphatic group, or R^2 and $R^{2'}$ are taken together 30 with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring; and

(d) each R^5 is independently selected from -halo, -CN, -NO₂, -N(R^4)₂, optionally substituted C₁₋₆

aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, or -N(R⁴)SO₂R.

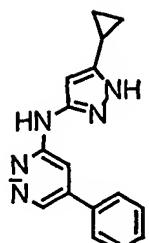
Even more preferred compounds of formula VIII have one or more, and more preferably all, of the
5 features selected from the group consisting of:

- (a) R^x is T-R³ wherein T is a valence bond or a methylene and R³ is -R or -OR wherein R is an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring;
- 10 (b) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R¹ is -halo, a C₁₋₄ aliphatic group optionally substituted with halogen, or -CN; or Ring D is an optionally
15 substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, quinolinyl, or
20 naphthyl;
- (c) R² and R^{2'} are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, -N(R⁴)₂, -C₁₋₄ alkyl,
25 -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, or -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group;
- 30 (d) each R⁵ is independently selected from -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic); and

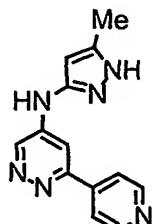
(e) R⁹ is R, OR, or N(R⁴)₂.

Representative compounds of formula VIII are set forth in Table 7 below.

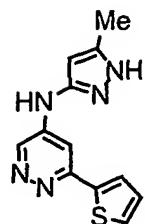
5 Table 7:



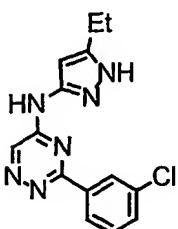
VIII-1



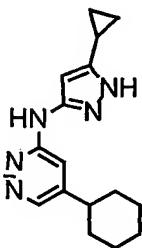
VIII-2



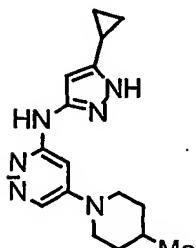
VIII-3



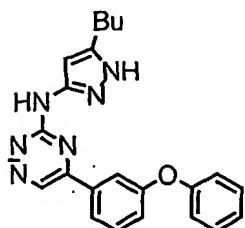
VIII-4



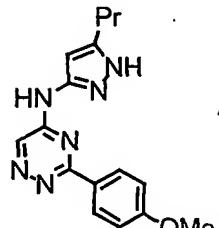
VIII-5



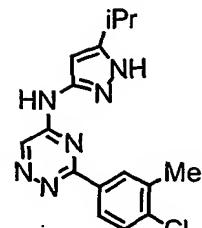
VIII-6



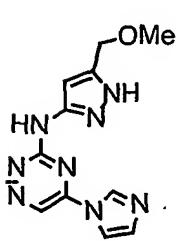
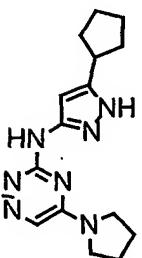
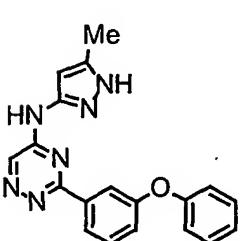
VIII-7



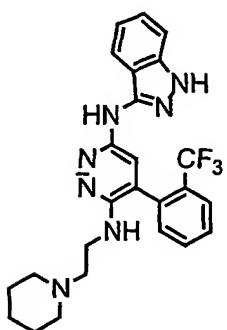
VIII-8



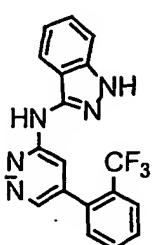
VIII-9



VIII-10



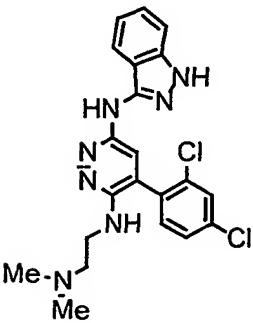
VIII-11



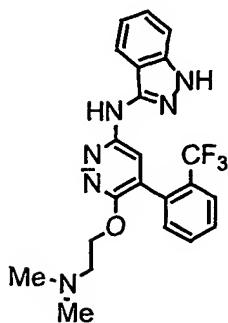
VIII-12



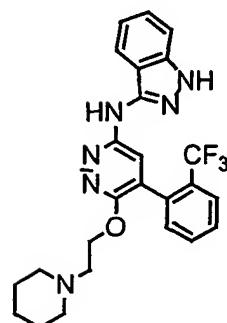
VIII-13



VIII-14

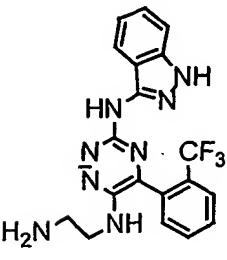


VIII-15

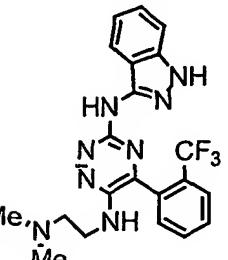


5

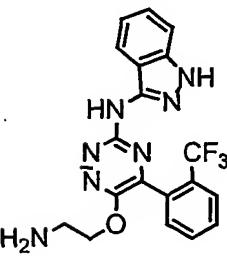
VIII-16



VIII-17

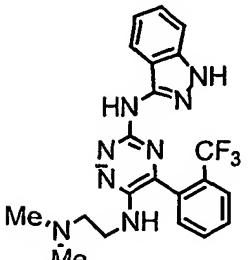
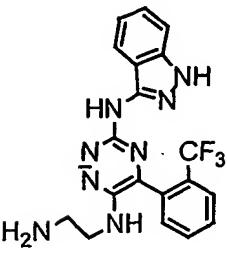


VIII-18

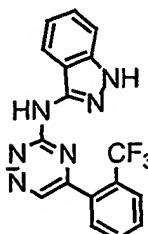


10

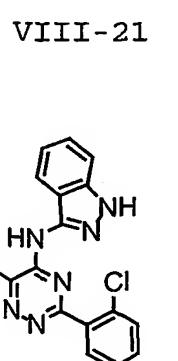
VIII-19

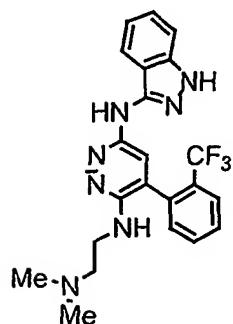
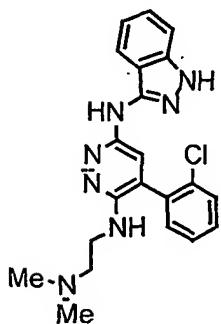
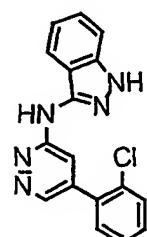
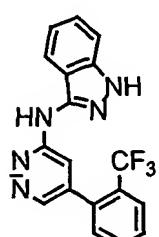
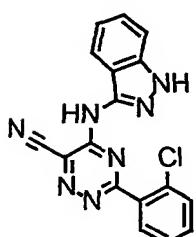
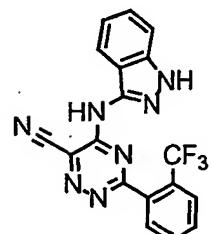
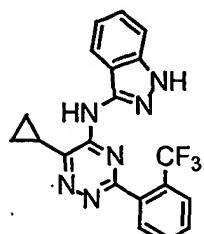
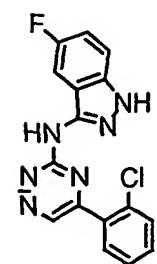
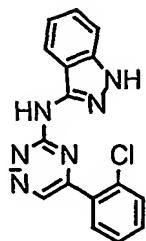


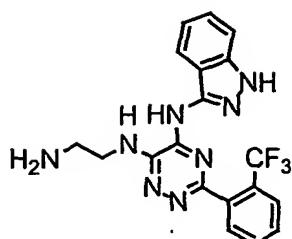
VIII-22



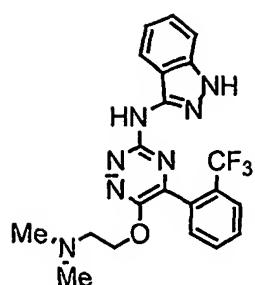
VIII-23



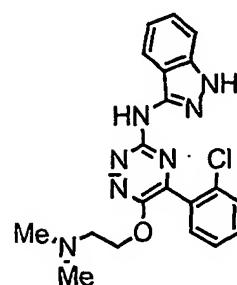




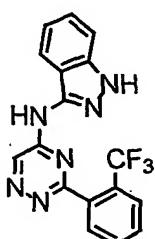
VIII-37



VIII-38

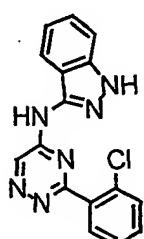


VIII-39

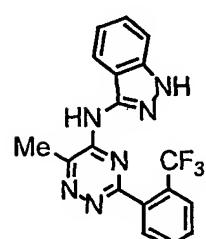


5

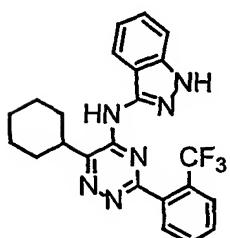
VIII-40



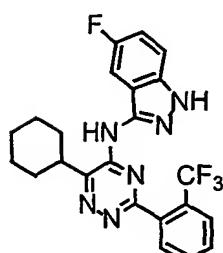
VIII-41



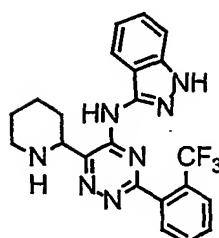
VIII-42



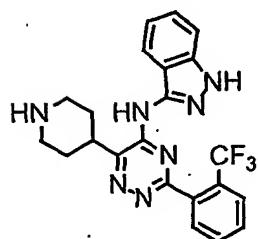
VIII-43



VIII-44

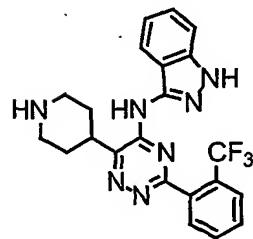


VIII-45

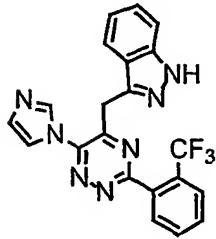


10

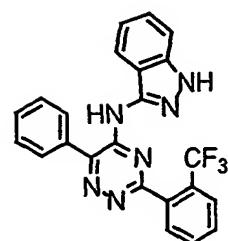
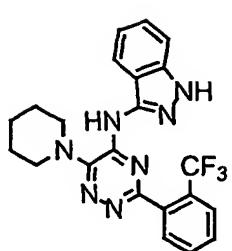
VIII-46



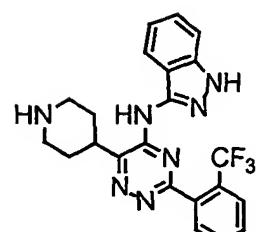
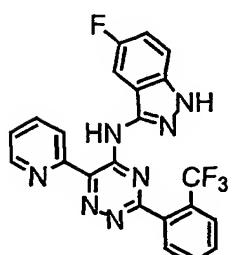
VIII-47



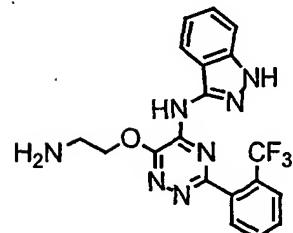
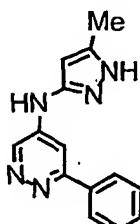
VIII-48



5



10



In another embodiment, this invention provides a composition comprising a compound of formula VIII and a pharmaceutically acceptable carrier.

One aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula VIII.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a GSK-3

inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula VIII.

5 Another aspect relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula
10 VIII. This method is especially useful for diabetic patients.

Another aspect relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising
15 administering to said patient a therapeutically effective amount of a composition comprising a compound of formula VIII. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

Another aspect relates to a method of
20 inhibiting the phosphorylation of β -catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula VIII. This method is especially useful for treating schizophrenia.

25 One aspect of this invention relates to a method of inhibiting Aurora activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula VIII.

30 Another aspect relates to a method of treating a disease that is alleviated by treatment with an Aurora inhibitor, said method comprising the step of administering to a patient in need of such a treatment a

therapeutically effective amount of a composition comprising a compound of formula VIII. This method is especially useful for treating cancer, such as colon, ovarian, and breast cancer.

5 One aspect of this invention relates to a method of inhibiting CDK-2 activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula VIII.

10 Another aspect relates to a method of treating a disease that is alleviated by treatment with a CDK-2 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula VIII. This method is especially useful for treating cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid 15 arthritis,

20

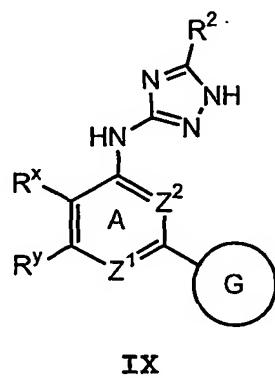
Another method relates to inhibiting GSK-3, Aurora, or CDK-2 activity in a biological sample, which method comprises contacting the biological sample with the GSK-3 or Aurora inhibitor of formula VIII, or a pharmaceutical composition thereof, in an amount 25 effective to inhibit GSK-3, Aurora or CDK-2.

Each of the aforementioned methods directed to the inhibition of GSK-3, Aurora or CDK-2, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula VIII, as 30 described above.

The above formula I compounds contain a pyrazole ring bearing the R² and R^{2'} substituents. In

their search for further inhibitors of the protein kinases GSK and Aurora, applicants sought to replace the pyrazole moiety of formula I with other heteroaromatic rings. One of the more effective pyrazole ring 5 replacements was found to be a triazole ring. Inhibitors having this triazole ring are otherwise structurally similar to the formula I compounds and are represented by the general formula IX:

10



or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

15 Z^1 is nitrogen or CR^9 and Z^2 is nitrogen or CH , provided that at least one of Z^1 and Z^2 is nitrogen;
 G is Ring C or Ring D;
 Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring,
 20 wherein said Ring C has one or two ortho substituents independently selected from $-R^1$, any substitutable non-ortho carbon position on Ring C is independently substituted by $-R^5$, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen,

said fused ring being optionally substituted by halo, oxo, or -R⁸;

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, 5 heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or -R⁵, and at any substitutable ring nitrogen by -R⁴, 10 provided that when Ring D is a six-membered aryl or heteroaryl ring, -R⁵ is hydrogen at each ortho carbon position of Ring D;

R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl 15 ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or -R⁸, said C₁₋₆ aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R¹ 20 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

R^x and R^y are independently selected from T-R³, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or T-R³, and any substitutable nitrogen on said ring formed by R^x and R^y is substituted by R⁴;

T is a valence bond or a C₁₋₄ alkylidene chain;

R² is -R or -T-W-R⁶;

R^3 is selected from -R, -halo, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)CO₂ (optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁷)₂;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or

5 heteroaryl ring;

each R⁵ is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂ (optionally substituted C₁₋₆ aliphatic),

10 -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, or R⁵ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

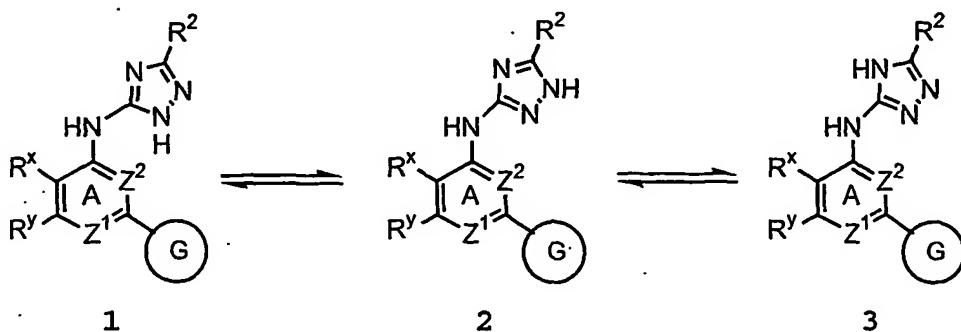
V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-,

15 -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-,

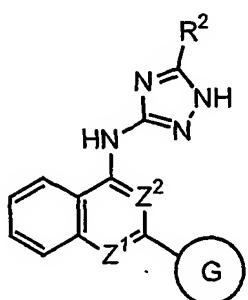
20 -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

W is $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$,
 $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-CO-$, $-CO_2-$,
 $-C(R^6)OC(O)-$, $-C(R^6)OC(O)N(R^6)-$, $-C(R^6)_2N(R^6)CO-$,
 $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$,
5 $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$,
 $-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;
each R^6 is independently selected from hydrogen, an
optionally substituted C_{1-4} aliphatic group, or two R^6
groups on the same nitrogen atom are taken together
10 with the nitrogen atom to form a 5-6 membered
 heterocyclyl or heteroaryl ring;
each R^7 is independently selected from hydrogen or an
optionally substituted C_{1-6} aliphatic group, or two R^7
on the same nitrogen are taken together with the
15 nitrogen to form a 5-8 membered heterocyclyl or
 heteroaryl ring;
each R^8 is independently selected from an optionally
substituted C_{1-4} aliphatic group, $-OR^6$, $-SR^6$, $-COR^6$,
 $-SO_2R^6$, $-N(R^6)_2$, $-N(R^6)N(R^6)_2$, $-CN$, $-NO_2$, $-CON(R^6)_2$, or
20 $-CO_2R^6$; and
 R^9 is selected from $-R$, halo, $-OR$, $-C(=O)R$, $-CO_2R$, $-COCOR$,
 $-NO_2$, $-CN$, $-S(O)R$, $-SO_2R$, $-SR$, $-N(R^4)_2$, $-CON(R^4)_2$,
 $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$ (optionally
substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$,
25 $-C=N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or
 $-OC(=O)N(R^4)_2$.

Compounds of formula IX may exist in
alternative tautomeric forms, as in tautomers 1-3 shown
below. Unless otherwise indicated, the representation of
30 any of these tautomers is meant to include the other two.

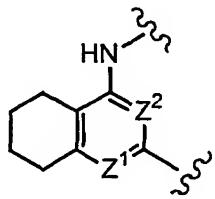


The R^x and R^y groups of formula IX may be taken
 5 together to form a fused ring, providing a bicyclic ring
 system containing Ring A. Preferred R^x/R^y rings include a
 5-, 6-, 7-, or 8-membered unsaturated or partially
 unsaturated ring having 0-2 heteroatoms, wherein said
 10 R^x/R^y ring is optionally substituted. Examples of Ring A
 systems are shown below by compounds IX-A through IX-DD,
 wherein Z^1 is nitrogen or $C(R^9)$ and Z^2 is nitrogen or
 C(H).

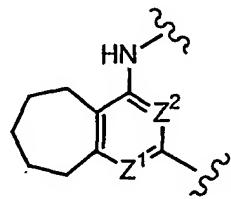


15

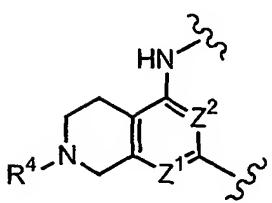
IX-A



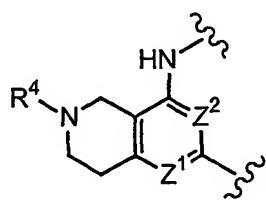
IX-B



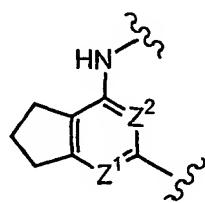
IX-C



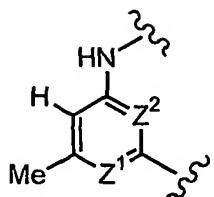
IX-D



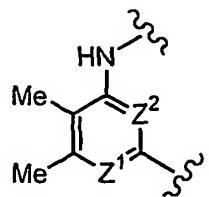
IX-E



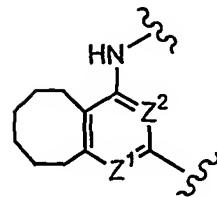
IX-F



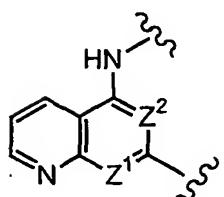
IX-G



IX-H

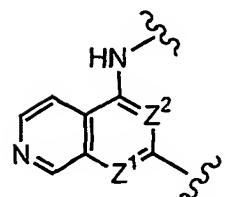


IX-I

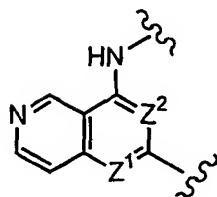


5

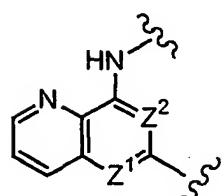
IX-J



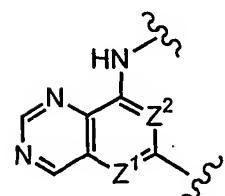
IX-K



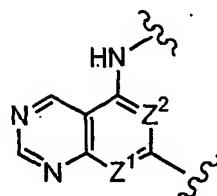
IX-L



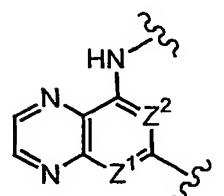
IX-M



IX-N

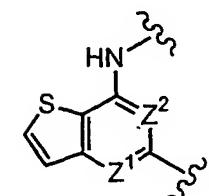


IX-O

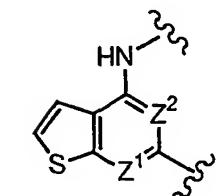


10

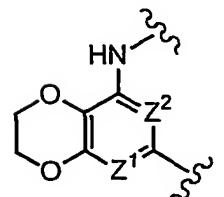
IX-P



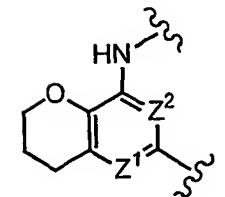
IX-Q



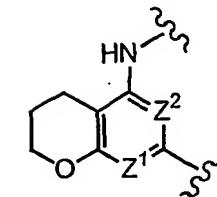
IX-R



IX-S

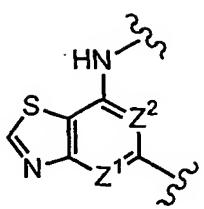


IX-T

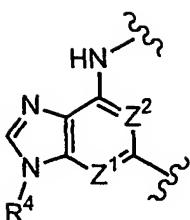


IX-U

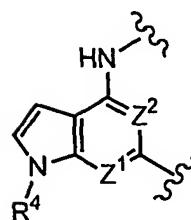
15



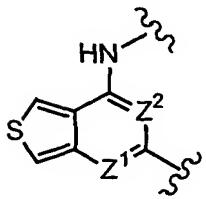
IX-V



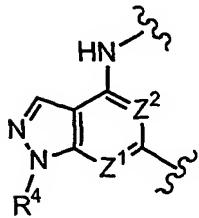
IX-W



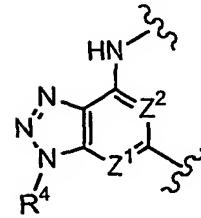
IX-X



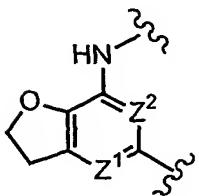
IX-Y



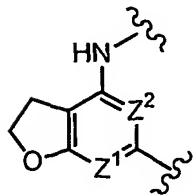
IX-Z



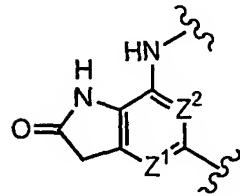
IX-AA



IX-BB



IX-CC



IX-DD

5

Preferred bicyclic Ring A systems of formula IX include IX-A, IX-B, IX-C, IX-D, IX-E, IX-F, IX-G, IX-H, 10 IX-I, IX-J, IX-K, IX-L, and IX-M, more preferably IX-A, IX-B, IX-C, IX-F, and IX-H, and most preferably IX-A, IX-B, and IX-H.

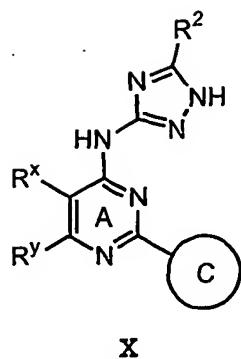
In the monocyclic Ring A system of formula IX, preferred R^x groups include hydrogen, alkyl- or 15 dialkylamino, acetamido, or a C₁₋₄ aliphatic group such as methyl, ethyl, cyclopropyl, isopropyl or t-butyl. Preferred R^y groups, when present, include T-R³ wherein T is a valence bond or a methylene, and R³ is -R, -N(R⁴)₂, or -OR. Examples of preferred R^y include 2-pyridyl, 4-pyridyl, piperidinyl, methyl, ethyl, cyclopropyl, 20 isopropyl, t-butyl, alkyl- or dialkylamino, acetamido, optionally substituted phenyl such as phenyl or halo-substituted phenyl, and methoxymethyl.

In the bicyclic Ring A system of formula IX, the ring formed by R^x and R^y taken together may be substituted or unsubstituted. Suitable substituents include -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, 5 -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, wherein R and R⁴ are as defined above.

10 Preferred R^x/R^y ring substituents include -halo, -R, -OR, -COR, -CO₂R, -CON(R⁴)₂, -CN, or -N(R⁴)₂ wherein R is an optionally substituted C₁₋₆ aliphatic group.

Preferred R² groups of formula IX include hydrogen, C₁₋₄ aliphatic, alkoxy carbonyl, (un)substituted 15 phenyl, hydroxyalkyl, alkoxyalkyl, aminocarbonyl, mono- or dialkylaminocarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonyl, and (N-heterocyclyl)carbonyl. Examples of such preferred R² substituents include methyl, cyclopropyl, ethyl, 20 isopropyl, propyl, t-butyl, cyclopentyl, phenyl, CO₂H, CO₂CH₃, CH₂OH, CH₂OCH₃, CH₂CH₂CH₂OH, CH₂CH₂CH₂OCH₃, CH₂CH₂CH₂OCH₂Ph, CH₂CH₂CH₂NH₂, CH₂CH₂CH₂NHCOOC(CH₃)₃, CONHCH(CH₃)₂, CONHCH₂CH=CH₂, CONHCH₂CH₂OCH₃, CONHCH₂Ph, CONH(cyclohexyl), CON(Et)₂, CON(CH₃)CH₂Ph, CONH(n-C₃H₇), 25 CON(Et)CH₂CH₂CH₃, CONHCH₂CH(CH₃)₂, CON(n-C₃H₇)₂, CO(3-methoxymethylpyrrolidin-1-yl), CONH(3-tolyl), CONH(4-tolyl), CONHCH₃, CO(morpholin-1-yl), CO(4-methylpiperazin-1-yl), CONHCH₂CH₂OH, CONH₂, and CO(piperidin-1-yl). A more preferred R² group for formula IX compounds is 30 hydrogen.

An embodiment that is particularly useful for treating GSK3-mediated diseases relates to compounds of formula X wherein ring A is a pyrimidine ring:



or a pharmaceutically acceptable derivative or prodrug thereof, wherein;

5 Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C has one or two ortho substituents independently selected from -R¹, any substitutable non-ortho carbon position on Ring C is independently substituted by -R⁵, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, 10 said fused ring being optionally substituted by halo, oxo, or -R⁸;

15 R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl, 20 and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or -R⁸, said C₁₋₆ aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R¹ and an adjacent substituent taken together with their 25 intervening atoms form said ring fused to Ring C;

R^x and R^y are independently selected from $T-R^3$, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or $T-R^3$, and any substitutable nitrogen on said ring formed by R^x and R^y is substituted by R^4 ;

T is a valence bond or a C_{1-4} alkylidene chain;

R^2 is $-R$ or $-T-W-R^6$;

R^3 is selected from $-R$, -halo, $-OR$, $-C(=O)R$, $-CO_2R$, $-COCOR$, $-COCH_2COR$, $-NO_2$, $-CN$, $-S(O)R$, $-S(O)_2R$, $-SR$, $-N(R^4)_2$, $-CON(R^7)_2$, $-SO_2N(R^7)_2$, $-OC(=O)R$, $-N(R^7)COR$, $-N(R^7)CO_2$ (optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^7)CON(R^7)_2$, $-N(R^7)SO_2N(R^7)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^7)_2$;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from $-R^7$, $-COR^7$, $-CO_2$ (optionally substituted C_{1-6} aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken

5 together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^5 is independently selected from $-R$, halo, $-OR$, $-C(=O)R$, $-CO_2R$, $-COCOR$, $-NO_2$, $-CN$, $-S(O)R$, $-SO_2R$, $-SR$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$ (optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$, or R^5 and

an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;

each R⁶ is independently selected from hydrogen, an optionally substituted C₁₋₄ aliphatic group, or two R⁶ groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

each R⁷ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R⁸ is independently selected from an optionally substituted C₁₋₄ aliphatic group, -OR⁶, -SR⁶, -COR⁶, -SO₂R⁶, -N(R⁶)₂, -N(R⁶)N(R⁶)₂, -CN, -NO₂, -CON(R⁶)₂, or -CO₂R⁶.

Compounds of formula X are structurally similar to compounds of formula II except for the replacement of the pyrazole ring moiety by the triazole ring moiety.

Preferred R², R^x, R^y and Ring C groups of formula X are as described above for the formula II compounds. Preferred formula X compounds have one or more, and more preferably all, of the features selected from the group consisting
5 of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a
10 naphthyl, quinolinyl or isoquinolinyl ring;

(b) R^x is hydrogen or C₁₋₄ aliphatic and R^y is T-R³, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted 5-7 membered unsaturated or partially unsaturated ring having 0-2 ring
15 nitrogen;

(c) R¹ is -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶; and
20 (d) R² is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C₁₋₆ aliphatic group.

More preferred compounds of formula X have one or more, and more preferably all, of the features
25 selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;
30 (b) R^x is hydrogen or methyl and R^y is -R, N(R⁴)₂, or -OR, or R^x and R^y are taken together with their intervening atoms to form a benzo ring or a 5-7 membered carbocyclo ring, wherein said ring formed by R^x and R^y is

optionally substituted with -R, halo, -OR, -C(=O)R, -CO₂R,
-COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂,
-SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂ (optionally
substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂,
5 -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or
-OC(=O)N(R⁴)₂;

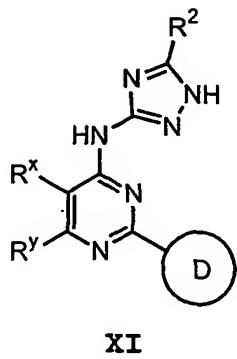
(c) R¹ is -halo, a C₁₋₆ haloaliphatic group, a C₁₋₆ aliphatic group, phenyl, or -CN;
10 (d) R² is hydrogen or a substituted or unsubstituted group selected from aryl or a C₁₋₆ aliphatic group; and
(e) each R⁵ is independently selected from -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR,
15 -SO₂N(R⁴)₂, or -N(R⁴)SO₂R.

Even more preferred compounds of formula X have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring,
20 optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;
(b) R^x is hydrogen or methyl and R^y is methyl, methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl,
25 alkyl- or an optionally substituted group selected from 2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted benzo ring or a 6-membered carbocyclo ring;
(c) R¹ is -halo, a C₁₋₄ aliphatic group optionally substituted with halogen, or -CN;
30 (d) R² is hydrogen or a C₁₋₆ aliphatic group; and

(e) each R⁵ is independently selected from -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic).

5 Another embodiment of this invention relates to compounds of formula XI:



10

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or -R⁵, and at any substitutable ring nitrogen by -R⁴, provided that when Ring D is a six-membered aryl or heteroaryl ring, -R⁵ is hydrogen at each ortho carbon position of Ring D;

R^x and R^y are taken together with their intervening atoms to form a fused benzo ring or 5-8 membered carbocyclo ring, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or T-R³; T is a valence bond or a C₁₋₄ alkylidene chain; R² is -R or -T-W-R⁶;

R^3 is selected from -R, -halo, =O, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R⁵ is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-,

-C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-,

-C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-,

-C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;

each R⁶ is independently selected from hydrogen or an

5 optionally substituted C₁₋₄ aliphatic group, or two R⁶ groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring; and

each R⁷ is independently selected from hydrogen or an
10 optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring.

Compounds of formula XI are structurally
15 similar to compounds of formula III except for the replacement of the pyrazole ring moiety by the triazole ring moiety. Preferred R², R^X, R^Y, and Ring D groups of formula XI are as described above for the formula III compounds. Preferred formula XI compounds have one or
20 more, and more preferably all, of the features selected from the group consisting of:

(a) Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^X and R^Y are taken together with their intervening atoms to form an optionally substituted benzo ring or 5-7 membered carbocyclo ring; and

(c) R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C_{1-6} aliphatic group.

More preferred compounds of formula XI have one
5 or more, and more preferably all, of the features
selected from the group consisting of:

(a) Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-
10 tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^x and R^y are taken together with their intervening atoms to form a benzo ring or 5-7 membered carbocyclo ring, wherein said ring formed by R^x and R^y is optionally substituted with -R, oxo, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂ (optionally substituted C_{1-6} aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

(c) R^2 is hydrogen or a substituted or unsubstituted group selected from aryl or a C_{1-6} aliphatic group; and

25 (d) each R^5 is independently selected from halo, oxo, CN, NO₂, -N(R⁴)₂, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -SR, -OR, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic.

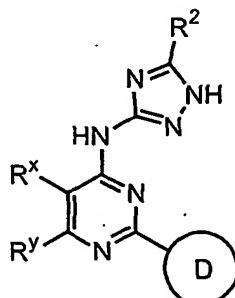
30 Even more preferred compounds of formula XI have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R^x and R^y are taken together with their intervening atoms to form a benzo ring or 6-membered carbocyclo ring, wherein said ring formed by R^x and R^y is optionally substituted with halo, CN, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, (C_{1-6} alkyl)carbonyl, (C_{1-6} alkyl)sulfonyl, mono- or dialkylamino, mono- or dialkylaminocarbonyl, mono- or dialkylaminocarbonyloxy, or 5-6 membered heteroaryl;

(b) each R^5 is independently selected from -halo, -CN, -oxo, -SR, -OR, -N(R^4)₂, -C(O)R, or a 10 substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C_{6-10} aryl, or C_{1-6} aliphatic; and
(c) R^2 is hydrogen or a C_{1-6} aliphatic group.

Another embodiment of this invention relates to compounds of formula XII:

15



XII

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

Ring D is a 5-7 membered monocyclic ring or 8-10 membered 20 bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or -R⁵, and at any substitutable ring nitrogen by -R⁴, 25 provided that when Ring D is a six-membered aryl or

heteroaryl ring, -R⁵ is hydrogen at each ortho carbon position of Ring D;

R^x and R^y are independently selected from T-R³, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 1-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring is optionally and independently substituted by T-R³, and any substitutable nitrogen on said ring is substituted by R⁴;

T is a valence bond or a C₁₋₄ alkylidene chain;

R² is -R or -T-W-R⁶;

R³ is selected from -R, -halo, =O, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷,

5 -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R⁵ is independently selected from -R, halo, -OR,

10 -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic),

$-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^4)CON(R^4)_2$,
 $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$;
 V is $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-N(R^6)SO_2-$, $-SO_2N(R^6)-$,
 $-N(R^6)-$, $-CO-$, $-CO_2-$, $-N(R^6)CO-$, $-N(R^6)C(O)O-$,
 5 $-N(R^6)CON(R^6)-$, $-N(R^6)SO_2N(R^6)-$, $-N(R^6)N(R^6)-$,
 $-C(O)N(R^6)-$, $-OC(O)N(R^6)-$, $-C(R^6)_2O-$, $-C(R^6)_2S-$,
 $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$,
 $-C(R^6)_2N(R^6)C(O)-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$,
 $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, or
 10 $-C(R^6)_2N(R^6)CON(R^6)-$;
 W is $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$,
 $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-CO-$, $-CO_2-$,
 $-C(R^6)OC(O)-$, $-C(R^6)OC(O)N(R^6)-$, $-C(R^6)_2N(R^6)CO-$,
 $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$,
 15 $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$,
 $-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;
 each R⁶ is independently selected from hydrogen or an
 optionally substituted C₁₋₄ aliphatic group, or two R⁶
 groups on the same nitrogen atom are taken together
 20 with the nitrogen atom to form a 5-6 membered
 heterocyclyl or heteroaryl ring; and
 each R⁷ is independently selected from hydrogen or an
 optionally substituted C₁₋₆ aliphatic group, or two R⁷
 on the same nitrogen are taken together with the
 25 nitrogen to form a 5-8 membered heterocyclyl ring or
 heteroaryl.

Compounds of formula XII are structurally
 similar to compounds of formula IV except for the
 replacement of the pyrazole ring moiety by the triazole
 30 ring moiety. Preferred R², R^x, R^y, and Ring D groups of
 formula XII are as described above for the formula IV
 compounds. Preferred formula XII compounds have one or

more, and more preferably all, of the features selected from the group consisting of:

(a) Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, 5 piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

10 (b) R^x is hydrogen or C₁₋₄ aliphatic and R^y is T-R³, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted 5-7 membered unsaturated or partially unsaturated ring having 1-2 ring heteroatoms; and

15 (c) R² is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C₁₋₆ aliphatic group.

More preferred compounds of formula XII have one or more, and more preferably all, of the features selected from the group consisting of:

(a) Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 25 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^x is hydrogen or methyl and R^y is -R, N(R⁴)₂, or -OR, or R^x and R^y are taken together with their intervening atoms to form a 5-7 membered unsaturated or 30 partially unsaturated ring having 1-2 ring nitrogens, wherein said ring is optionally substituted with -R, halo, oxo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R,

-N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

5 (c) R² is hydrogen or a substituted or unsubstituted group selected from aryl or a C₁₋₆ aliphatic group; and

10 (d) each R⁵ is independently selected from halo, oxo, CN, NO₂, -N(R⁴)₂, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -SR, -OR, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic.

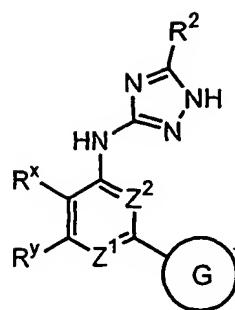
Even more preferred compounds of formula XII have one or more, and more preferably all, of the features selected from the group consisting of:

15 (a) R^x and R^y are taken together with their intervening atoms to form a 6-membered unsaturated or partially unsaturated ring having 1-2 ring nitrogens, optionally substituted with halo, CN, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, (C₁₋₆ alkyl)carbonyl, (C₁₋₆ alkyl)sulfonyl, mono- or 20 dialkylamino, mono- or dialkylaminocarbonyl, mono- or dialkylaminocarbonyloxy; or 5-6 membered heteroaryl;

25 (b) each R⁵ is independently selected from -halo, -CN, -oxo, -SR, -OR, -N(R⁴)₂, -C(O)R, or a substituted or unsubstituted group selected from 5-6 membered heterocyclyl, C₆₋₁₀ aryl, or C₁₋₆ aliphatic; and

(c) R² is hydrogen or a C₁₋₆ aliphatic group.

Another embodiment of this invention relates to compounds of formula XIII:



XIII

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

Z^1 is nitrogen, CR^a , or CH , and Z^2 is nitrogen or CH ;
provided that one of Z^1 and Z^2 is nitrogen;

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl,
5 pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring,
wherein said Ring C has one or two ortho substituents
independently selected from $-R^1$, any substitutable non-
ortho carbon position on Ring C is independently
substituted by $-R^5$, and two adjacent substituents on
10 Ring C are optionally taken together with their
intervening atoms to form a fused, unsaturated or
partially unsaturated, 5-6 membered ring having 0-3
heteroatoms selected from oxygen, sulfur or nitrogen,
said fused ring being optionally substituted by halo,
15 oxo, or $-R^8$;

Ring D is a 5-7 membered monocyclic ring or 8-10 membered
bicyclic ring selected from aryl, heteroaryl,
heterocyclyl or carbocyclyl, said heteroaryl or
heterocyclyl ring having 1-4 ring heteroatoms selected
20 from nitrogen, oxygen or sulfur, wherein Ring D is
substituted at any substitutable ring carbon by oxo or
 $-R^5$, and at any substitutable ring nitrogen by $-R^4$,
provided that when Ring D is a six-membered aryl or

heteroaryl ring, -R⁵ is hydrogen at each ortho carbon position of Ring D;

R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or -R⁸, said C₁₋₆ aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R¹ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

10 R^x and R^y are independently selected from T-R³, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or T-R³, and any substitutable nitrogen on said ring formed by R^x and R^y is substituted by R⁴;

T is a valence bond or a C₁₋₄ alkylidene chain;

R² is -R or -T-W-R⁶;

R³ is selected from -R, -halo, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁷)₂;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or

5 heteroaryl ring;

each R⁵ is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic),

10 -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, or R⁵ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-,-SO₂N(R⁶)-,

15 -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-,

20 -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-,

25 -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;

each R⁶ is independently selected from hydrogen, an optionally substituted C₁₋₄ aliphatic group, or two R⁶ groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

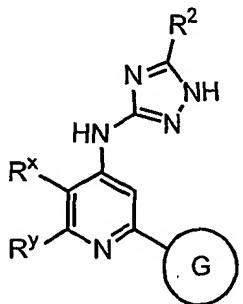
each R⁷ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring;

5 each R⁸ is independently selected from an optionally substituted C₁₋₄ aliphatic group, -OR⁶, -SR⁶, -COR⁶, -SO₂R⁶, -N(R⁶)₂, -N(R⁶)N(R⁶)₂, -CN, -NO₂, -CON(R⁶)₂, or -CO₂R⁶; and

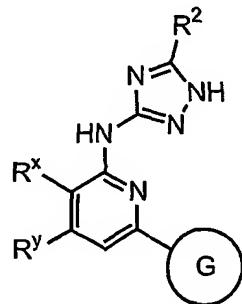
10 R^a is selected from halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, -OC(=O)N(R⁴)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms.

15

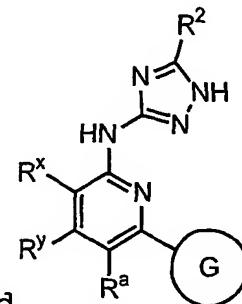
Compounds of formula XIII may be represented by specifying Z¹ and Z² as shown below:



XIIIa



XIIIb



XIIIc

25 Compounds of formula XIII are structurally similar to compounds of formula V except for the replacement of the pyrazole ring moiety by the triazole ring moiety. Preferred R², R^x, R^y, R^a, and Ring G groups

of formula **XIII** are as described above for the formula **V** compounds. Preferred formula **XIII** compounds have one or more, and more preferably all, of the features selected from the group consisting of:

5 (a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring, and R¹ is
10 -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶; or Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl,
15 thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;
20 (b) R^x is hydrogen or C₁₋₄ aliphatic and R^y is T-R³, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted 5-7 membered unsaturated or partially unsaturated ring having 0-2 ring nitrogens; and
25 (c) R² is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C₁₋₆ aliphatic group.

More preferred compounds of formula **XIII** have one or more, and more preferably all, of the features selected from the group consisting of:

30 (a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and

R¹ is -halo, a C₁₋₆ haloaliphatic group, a C₁₋₆ aliphatic group, phenyl, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 5 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-isoindolyl, 2,3-dihydro-1H-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^x is hydrogen or methyl and R^y is -R,
 10 N(R⁴)₂, or -OR, or R^x and R^y are taken together with their intervening atoms to form a benzo ring or a 5-7 membered carbocyclo ring, wherein said ring formed by R^x and R^y is optionally substituted with -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂,
 15 -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

(c) R² is hydrogen or a substituted or
 20 unsubstituted group selected from aryl, or a C₁₋₆ aliphatic group; and

(d) each R⁵ is independently selected from -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR,
 25 -SO₂N(R⁴)₂, or -N(R⁴)SO₂R, and, when Ring G is Ring D, Ring D is substituted by oxo or R⁵.

Even more preferred compounds of formula XIII have one or more, and more preferably all, of the features selected from the group consisting of:

30 (a) R^x is hydrogen or methyl and R^y is methyl, methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or an optionally substituted group selected from 2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^x and R^y

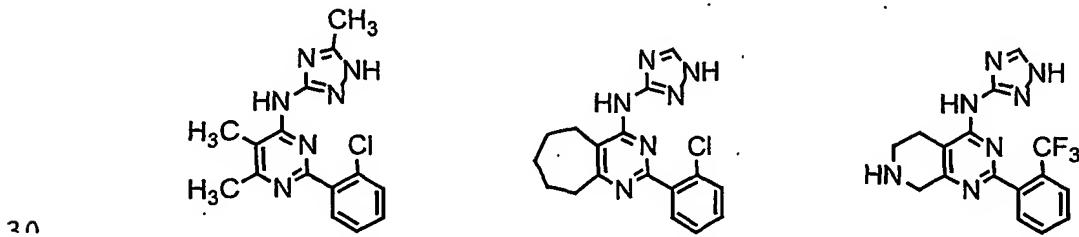
are taken together with their intervening atoms to form a benzo ring or a 6-membered carbocyclo ring wherein said ring formed by R^x and R^y is optionally substituted with halo, CN, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, (C₁₋₆ alkyl)carbonyl, (C₁₋₆ alkyl)sulfonyl, mono- or dialkylamino, mono- or dialkylaminocarbonyl, mono- or dialkylaminocarbonyloxy, or 5-6 membered heteroaryl;

5 (b) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R¹ is -halo, a C₁₋₄ aliphatic group optionally substituted with halogen, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, quinolinyl, or naphthyl;

10 (c) R² is hydrogen or a C₁₋₆ aliphatic group; and
 15 (d) each R⁵ is independently selected from -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic), and when Ring G is Ring D, Ring D is substituted by oxo or R⁵.

20 25 Representative compounds of formula IX are shown below in Table 8.

Table 8.



IX-1



IX-2



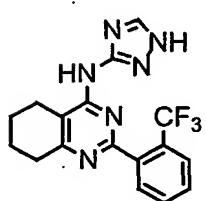
IX-3



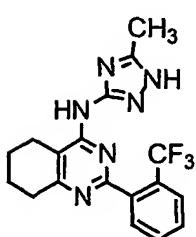
IX-4

IX-6

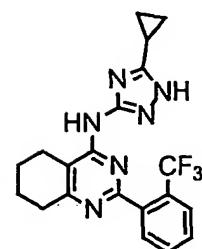
5



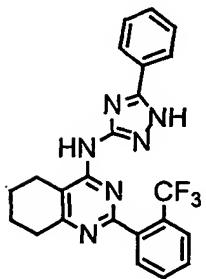
IX-7



IX-8

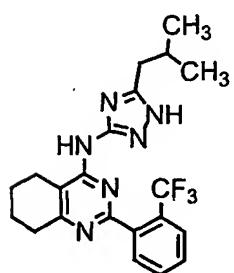


IX-9

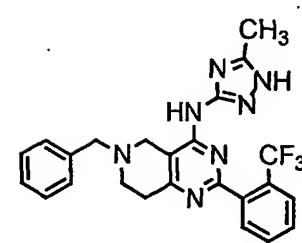


10

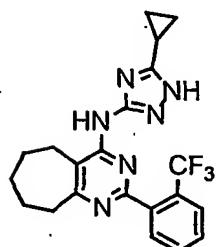
IX-10



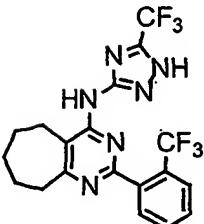
IX-11



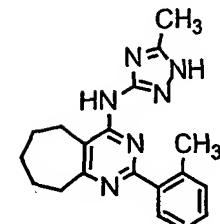
IX-12



IX-13

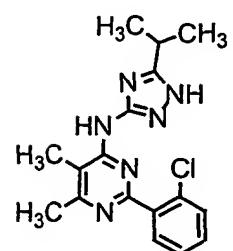
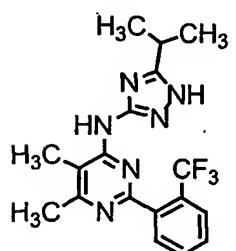
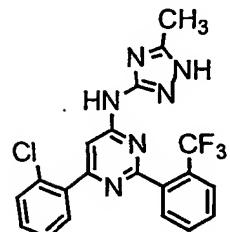
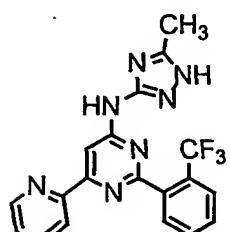
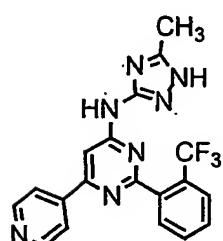
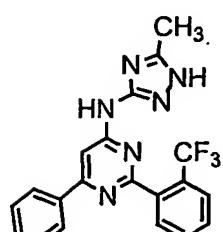
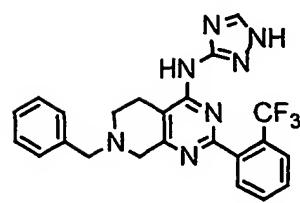
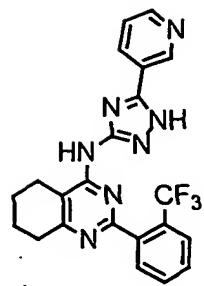
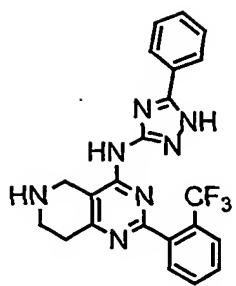


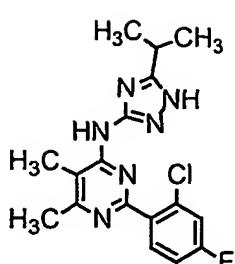
IX-14



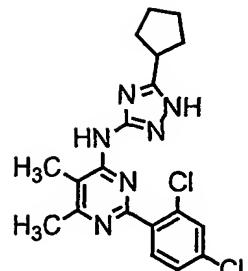
IX-15

15





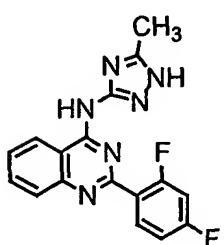
IX-28



IX-29

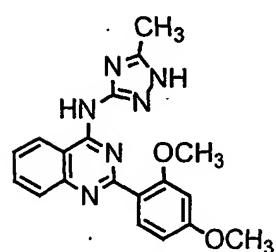


IX-30

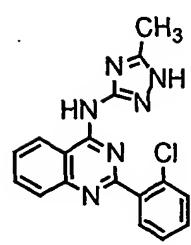


5

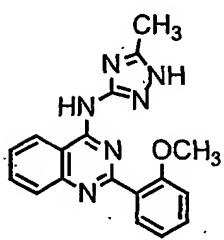
IX-31



IX-32



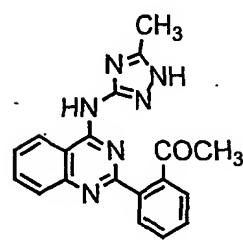
IX-33



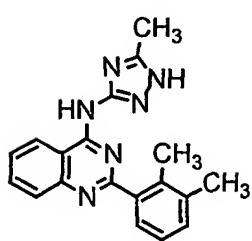
IX-34



IX-35



IX-36

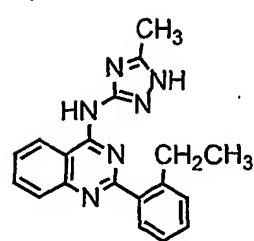


10

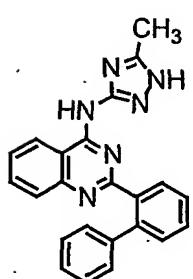
IX-37



IX-38



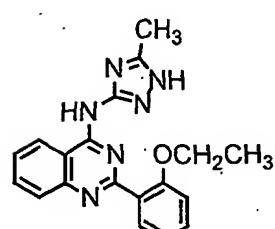
IX-39



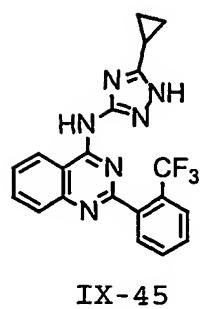
IX-40



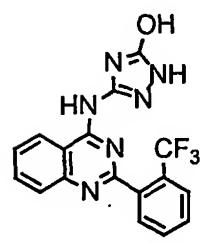
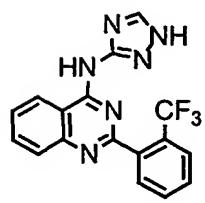
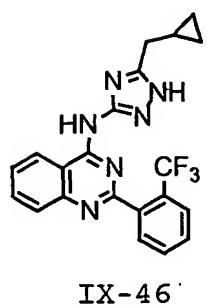
IX-41



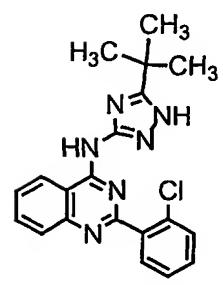
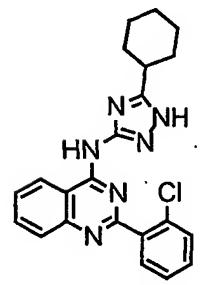
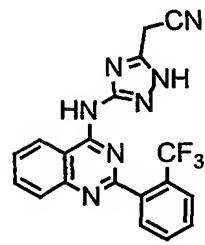
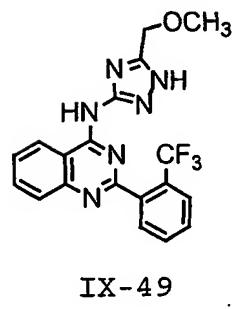
IX-42

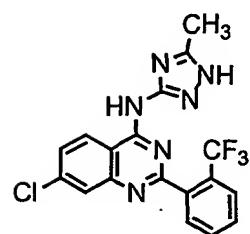
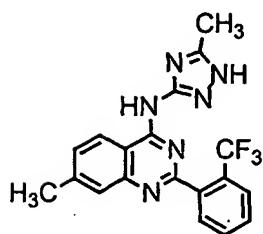
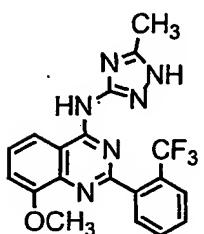
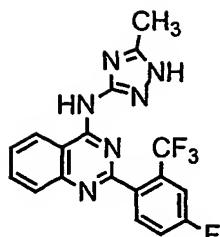


5

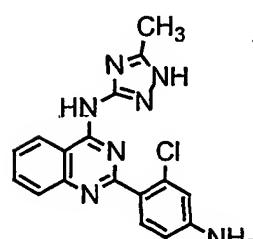
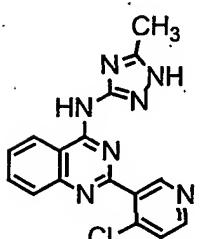


10

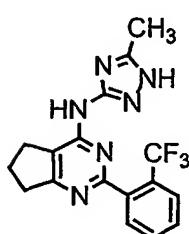
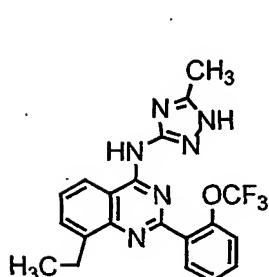
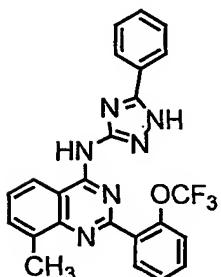


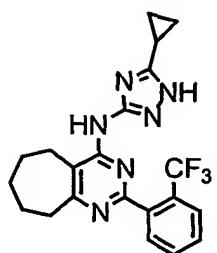


5

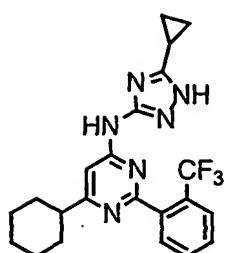


10

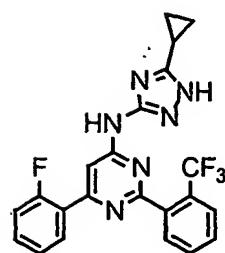




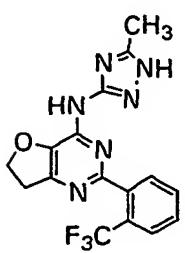
IX-70



IX-71

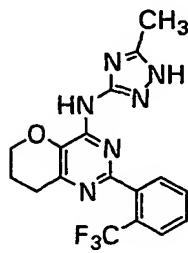


IX-72

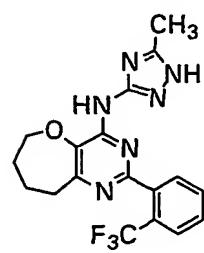


5

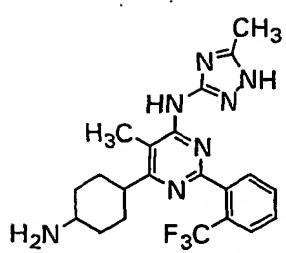
IX-73



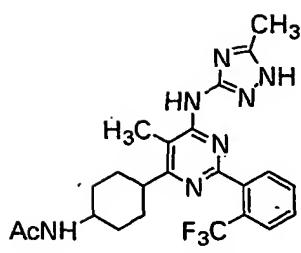
IX-74



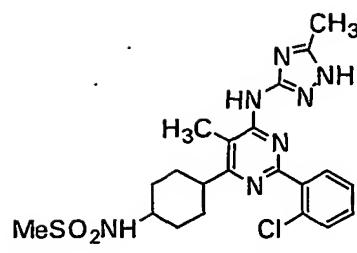
IX-75



IX-76

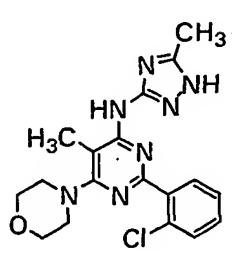


IX-77

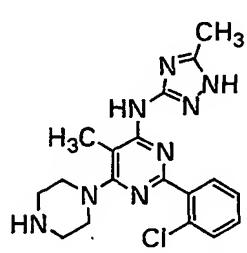


IX-78

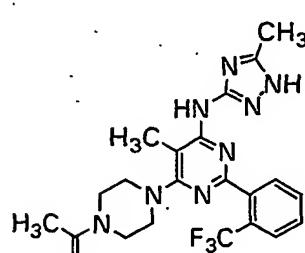
10



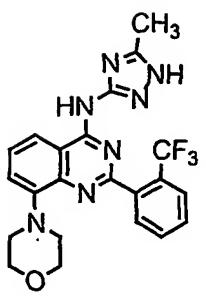
IX-79



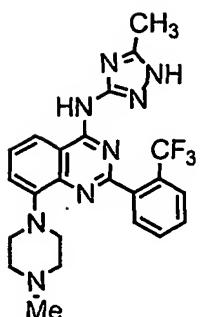
IX-80



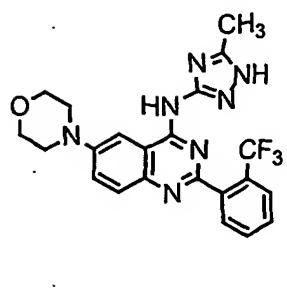
IX-81



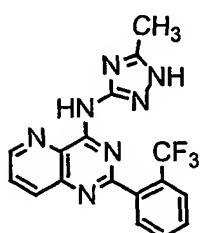
IX-82



IX-83

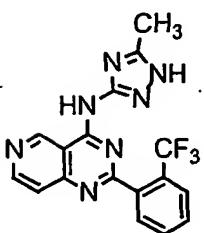


IX-84



5

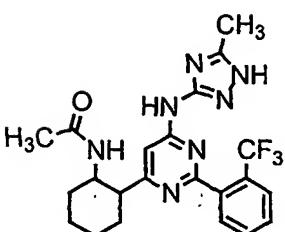
IX-85



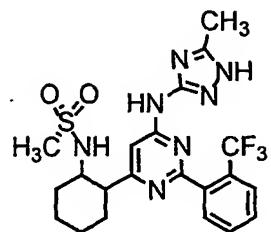
IX-86



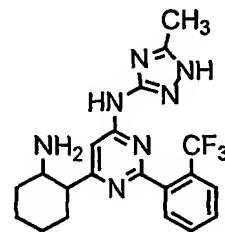
IX-87



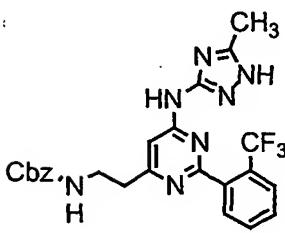
IX-88



IX-89

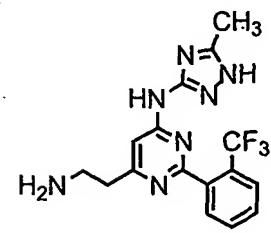


IX-90

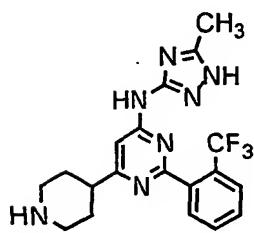


10

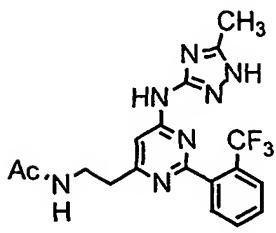
IX-91



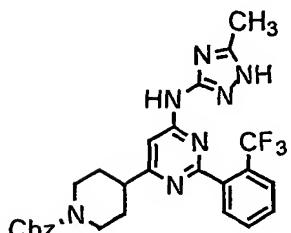
IX-92



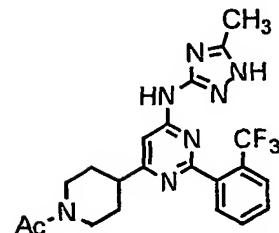
IX-93



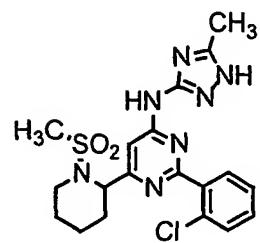
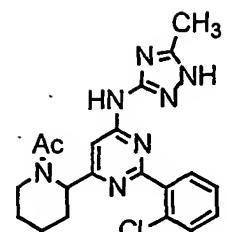
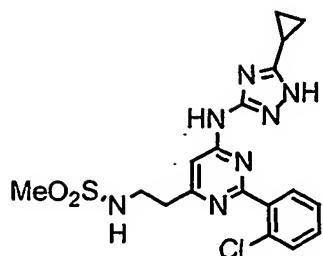
IX-94



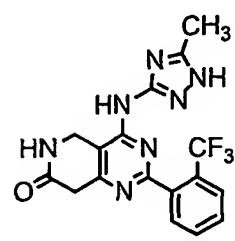
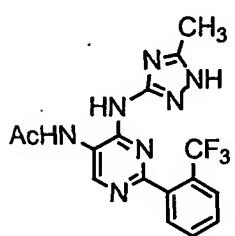
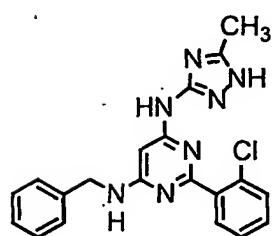
IX-95



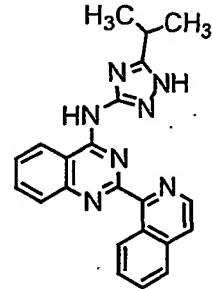
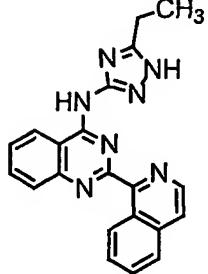
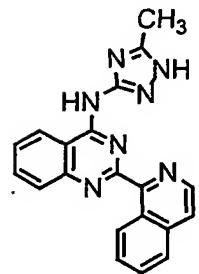
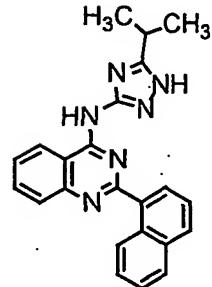
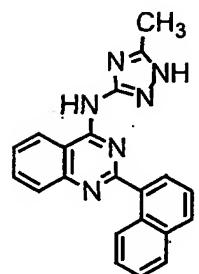
IX-96

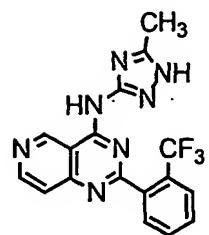
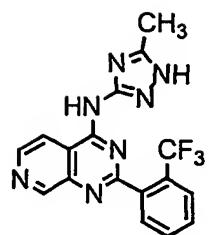
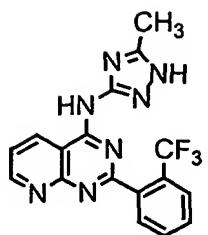


5

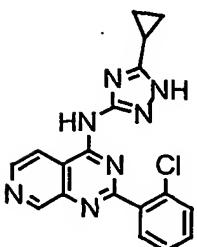


10

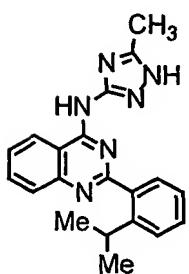




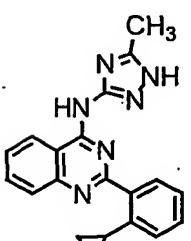
5



5

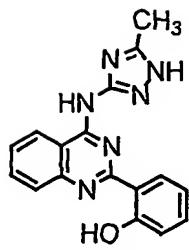


10





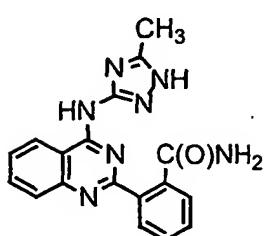
IX-121



IX-122



IX-123

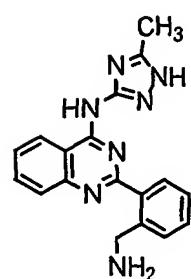


5

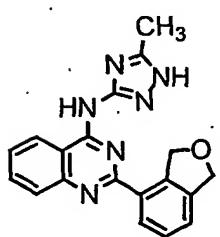
IX-124



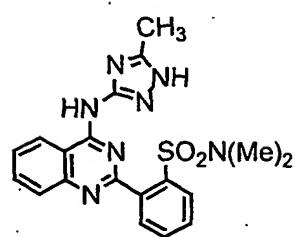
IX-125



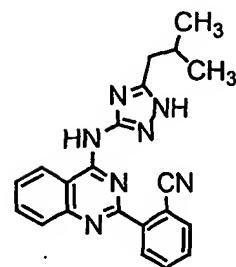
IX-126



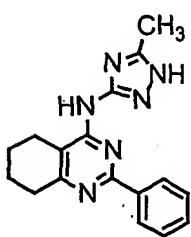
IX-127



IX-128

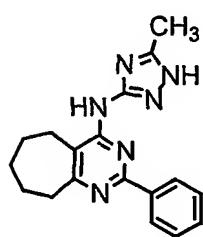


IX-129



10

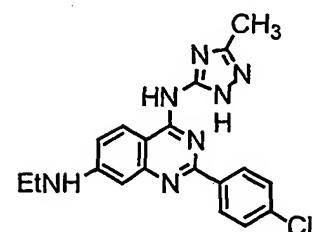
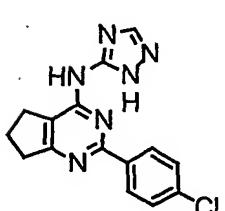
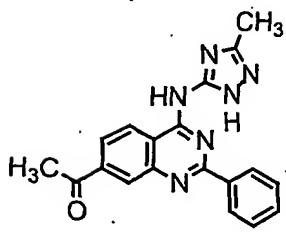
IX-130



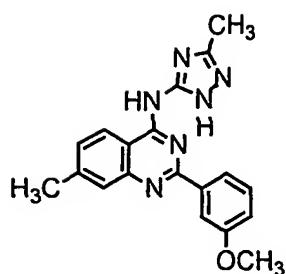
IX-131



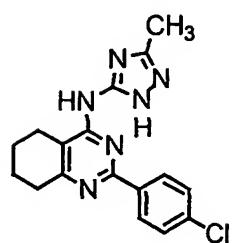
IX-132



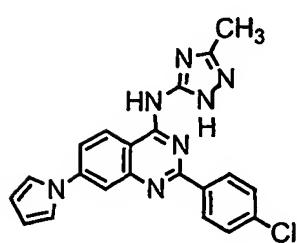
IX-133



IX-134

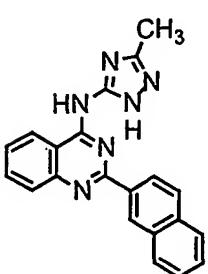


IX-135

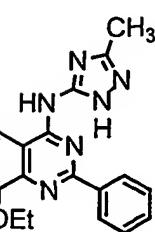


IX-136

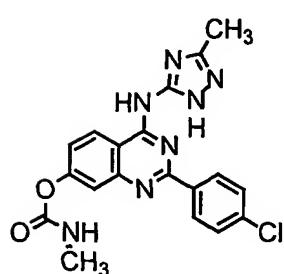
5



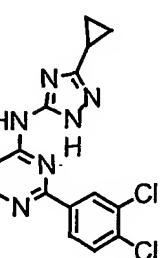
IX-137



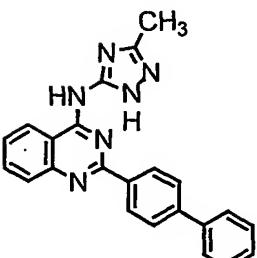
IX-138



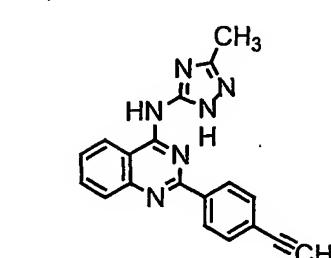
IX-139



IX-140

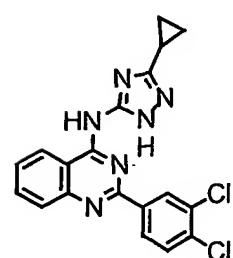


IX-141

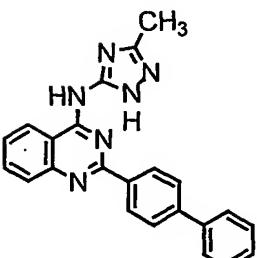


10

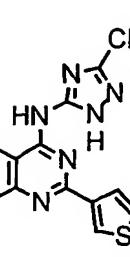
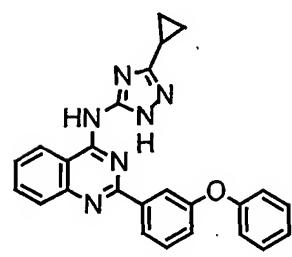
IX-142



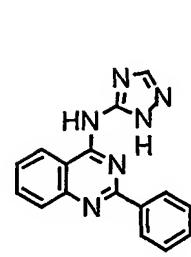
IX-143



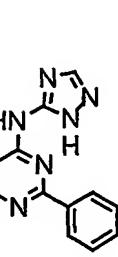
IX-144



IX-145

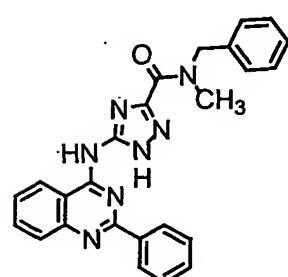
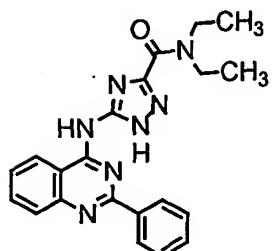
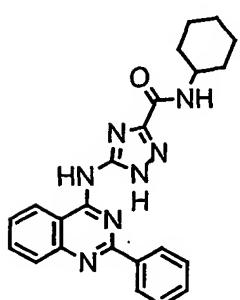
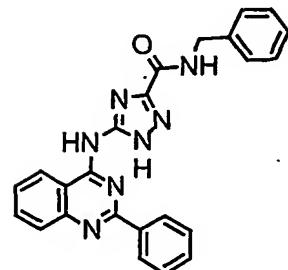
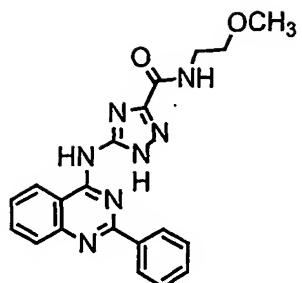
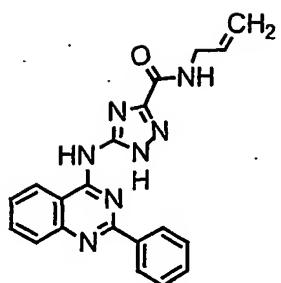


IX-146

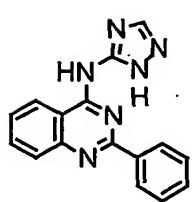


IX-147

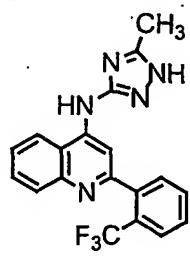
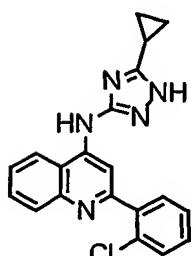
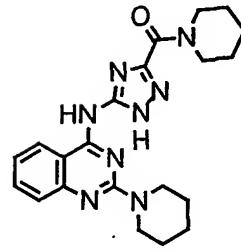
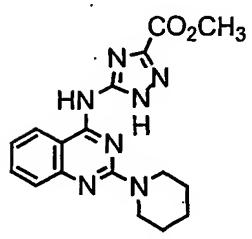
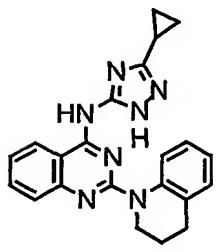
15



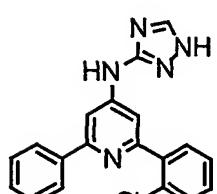
5



10

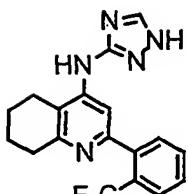


IX-160



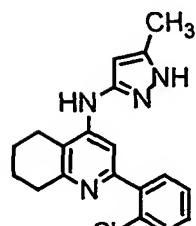
IX-163

IX-161



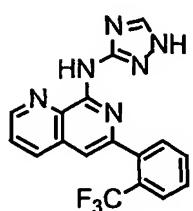
IX-164

IX-162



IX-165

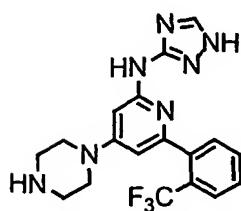
5



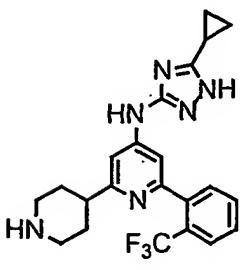
IX-166



IX-167

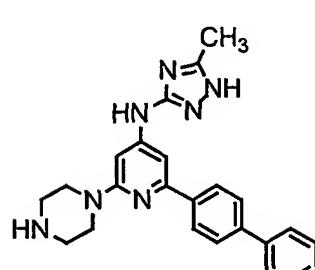


IX-168

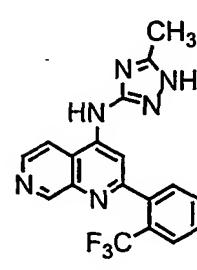


10

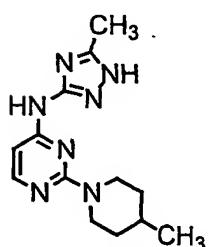
IX-169



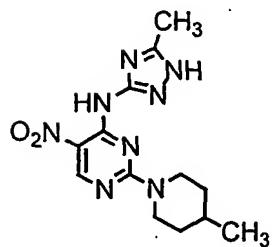
IX-170



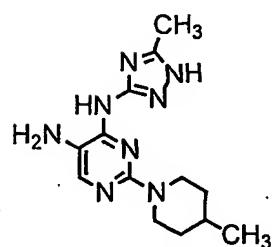
IX-171



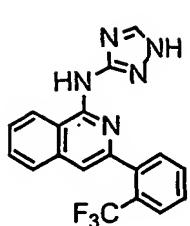
IX-172



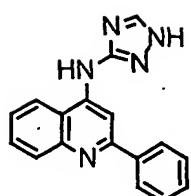
IX-173



IX-174



IX-175



IX-176



IX-177

In another embodiment, this invention provides
5 a composition comprising a compound of formula IX and a pharmaceutically acceptable carrier.

One aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, comprising administering to the patient a therapeutically 10 effective amount of a composition comprising a compound of formula IX.

Another aspect relates to a method of treating a disease that is alleviated by treatment with a GSK-3 inhibitor, said method comprising the step of 15 administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula IX.

Another aspect relates to a method of enhancing glycogen synthesis and/or lowering blood levels of 20 glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula IX. This method is especially useful for diabetic patients.

25 Another aspect relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula

IX. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

Another aspect relates to a method of inhibiting the phosphorylation of β -catenin in a patient 5 in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula IX. This method is especially useful for treating schizophrenia.

One aspect of this invention relates to a 10 method of inhibiting Aurora activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a compound of formula IX.

Another aspect relates to a method of treating 15 a disease that is alleviated by treatment with an Aurora inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of a composition comprising a compound of formula IX. This method is especially useful for treating cancer, such as colon, ovarian, and breast cancer.

20 Another method relates to inhibiting GSK-3 or Aurora activity in a biological sample, which method comprises contacting the biological sample with the GSK-3 or Aurora inhibitor of formula IX, or a pharmaceutical composition thereof, in an amount effective to inhibit GSK-3 or Aurora.

Each of the aforementioned compositions and 30 methods directed to the inhibition of GSK-3 or Aurora, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula IX, as described above.

The compounds of this invention may be prepared as illustrated by the Synthetic Methods below, by the Synthetic Examples described herein and by general methods known to those skilled in the art.

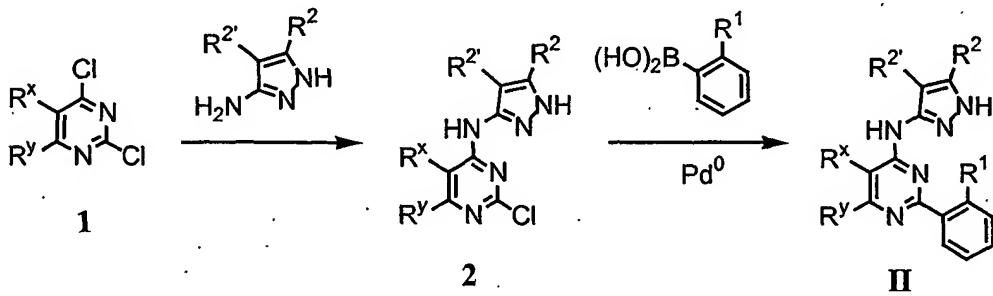
5

General Synthetic Methods

The general synthetic methods below provide a series of general reaction routes that were used to prepare compounds of this invention. Methods A-F below are particularly useful for preparing formula II compounds. In most cases, Ring C is drawn as a phenyl ring bearing an ortho R¹ substituent. However, it will be apparent to one skilled in the art that compounds having other Ring C groups may be obtained in a similar manner.

Methods analogous to methods A-F are also useful for preparing other compounds of this invention. Methods F-I below are particularly useful for preparing compounds of formula III or IV.

Method A



Method A is a general route for the preparation of compounds wherein ring C is an aryl or heteroaryl ring. Preparation of the starting dichloropyrimidine 1 may be achieved in a manner similar to that described in *Chem. Pharm. Bull.*, 30, 9, 1982, 3121-3124. The chlorine in position 4 of intermediate 1 may be replaced by an aminopyrazole or aminoindazole to provide intermediate 2

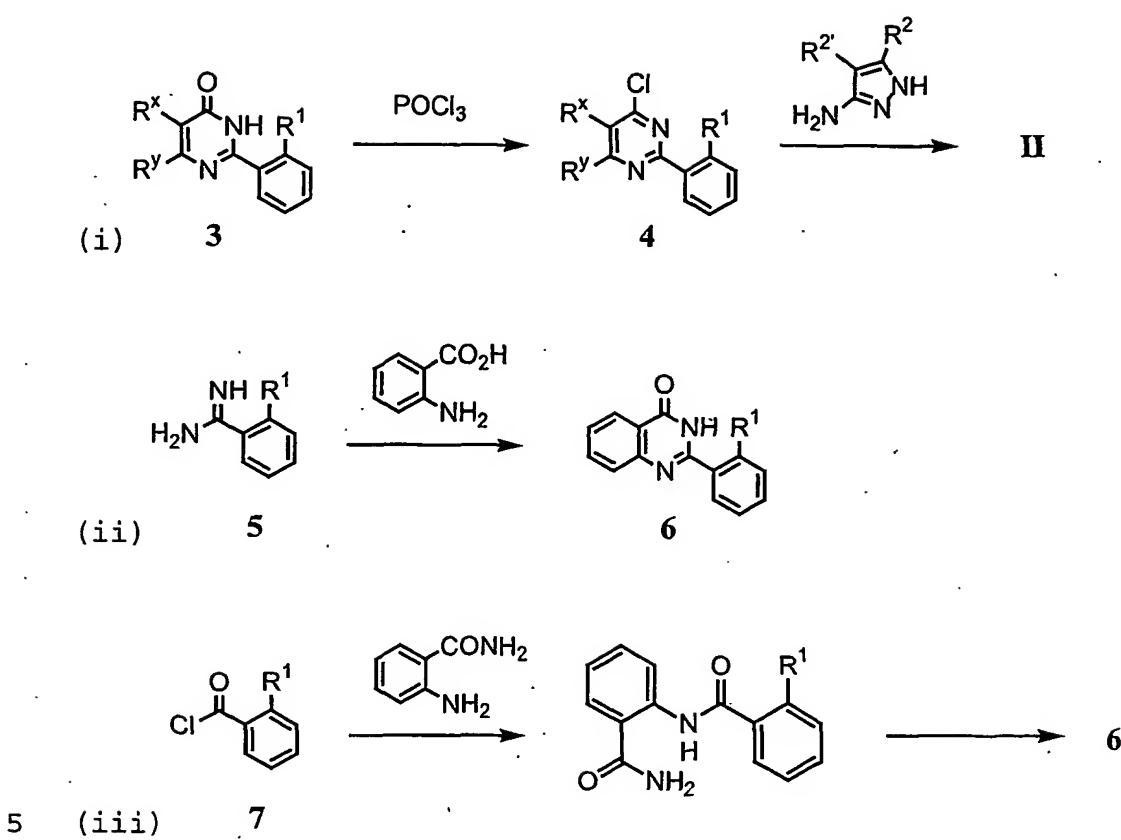
in a manner similar to that described in *J. Med. Chem.*, 38, 3547-3557 (1995). Ring C is then introduced using a boronic ester under palladium catalysis (see *Tetrahedron*, 48, 37, 1992, 8117-8126). This method is illustrated by
5 the following procedure.

A suspension of 1*H*-quinazoline-2,4-dione (10.0 g, 61.7 mmol) in POCl₃ (60 mL, 644 mmol) and N,N-dimethylaniline (8mL, 63.1 mmol) is heated under reflux for 2 h. Excess POCl₃ is evaporated under vacuum, the
10 residue is poured into ice, and the precipitate is collected by filtration. The crude solid 2,4-dichloroquinazoline product may be used without further purification.

To a solution of 2,4-dichloro-quinazoline (3.3 g, 16.6 mmol) in anhydrous ethanol (150 mL) is added 5-methyl-1*H*-pyrazol-3-yl amine (3.2 g, 32.9 mmol). The mixture is stirred at room temperature for 4 h, and the resulting precipitate is collected by filtration, washed with ethanol, and dried under vacuum to afford (2-chloro-
20 quinazolin-4-yl)-(5-methyl-1*H*-pyrazol-3-yl)-amine.

To a solution of (2-chloro-quinazolin-4-yl)-(5-methyl-1*H*-pyrazol-3-yl)-amine (50 mg, 0.19 mmol) in DMF (1.0 mL) is added the desired arylboronic acid (0.38 mmol), 2M Na₂CO₃ (0.96 mmol), and tri-*t*-butylphosphine
25 (0.19 mmol). Under nitrogen, PdCl₂(dppf) (0.011 mmol) is added in one portion. The reaction mixture is then heated at 80°C for 5 to 10 hours, cooled to room temperature, and poured into water (2 mL). The resulting precipitate is collected by filtration, washed with
30 water, and purified by HPLC.

Method B



Methods B through F describe routes where the pyrazole ring system is introduced after Ring C and the pyrimidine ring portion are first constructed. A 10 versatile intermediate is the 4-chloropyrimidine 4, which is readily obtained from pyrimidinone 3 as shown in Method B(i). This reaction sequence is generally applicable for a variety of Ring C groups including aliphatic, aryl, heteroaryl, or heterocyclyl. See J. 15 Med. Chem., 38, 3547-3557 (1995).

For quinazoline ring systems (where R^x and R^y are taken together to form a benzo ring), the useful intermediate 6 may be obtained by condensing an anthranilic acid or its derivative with a benzamidine as shown in Method B(ii) or by condensing a benzoylchloride with an anthranilamide as shown in Method B(iii). Many substituted anthranilic acid, anthranilamide, benzamidine and benzoylchloride starting materials may be obtained by

known methods. See *Aust. J. Chem.*, 38, 467-474 and *J. Med. Chem.*, 38, 3547-3557 (1995). Method B(iii) is illustrated by the following procedure.

To a solution of anthranilamide (33 mmol) in
5 THF and CH₂Cl₂ (1:1, 70 mL) is added the desired
benzoylchloride (33 mmol), and triethylamine (99 mmol) at
room temperature. The mixture is stirred for about 14
hours. The resulting precipitate is collected by
filtration, washed with CH₂Cl₂ and water, and dried under
10 vacuum. The crude 2-benzoylaminobenzamide may be used
directly for the next step without further purification.

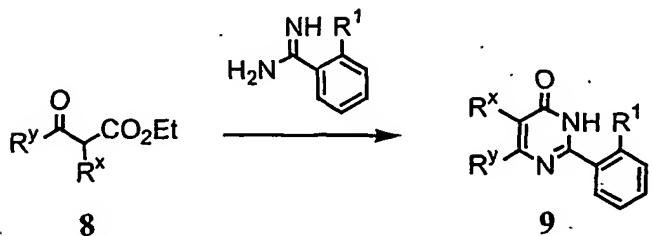
To a solution of the above crude product (13
mmol) in ethanol (50 mL) is added NaOEt (26 mmol) at room
temperature. The mixture is heated under reflux for 48
15 to 96 h. The solvent is evaporated and the residue is
neutralized using concentrated HCl to pH 7. The product
is then collected by filtration and dried under vacuum to
provide 2-phenyl-3H-quinazolin-4-one that may be used
without further purification.

20 To a suspension of the above product (12 mmol)
in POCl₃ (120 mmol) is added tri-n-propylamine (24 mmol).
The mixture is heated under reflux for 1h. After removal
of the excess POCl₃ by evaporation, the residue is
dissolved in ethyl acetate, and washed with 1N NaOH
25 (twice) and water (twice). The organic layer is dried
over MgSO₄, the solvent is evaporated under vacuum, and
the crude product is purified by flash chromatography
(eluting with 10% of ethyl acetate in hexanes) to give
4-chloro-2-aryl quinazoline.

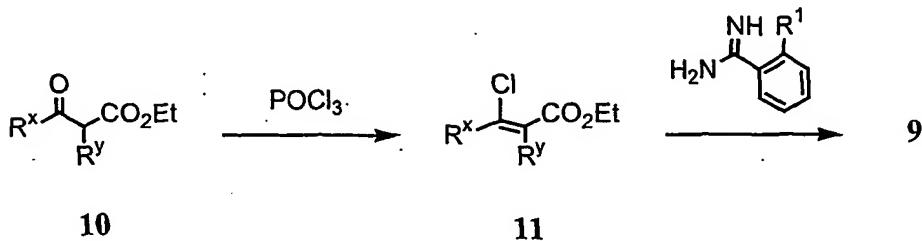
30 To a solution of 4-chloro-2-aryl quinazoline
(0.16 mmol) in DMF (or THF, ethanol) (1 mL) is added the
desired aminopyrazole or aminoindazole (0.32 mmol). The
mixture is heated in DMF (or THF under reflux) at 100 to

110°C for 16 h (or in ethanol at 130-160°C for 16 hours) and then poured into water (2 mL). The precipitate is collected by filtration and purified by HPLC.

5 Method C



Method D(i)



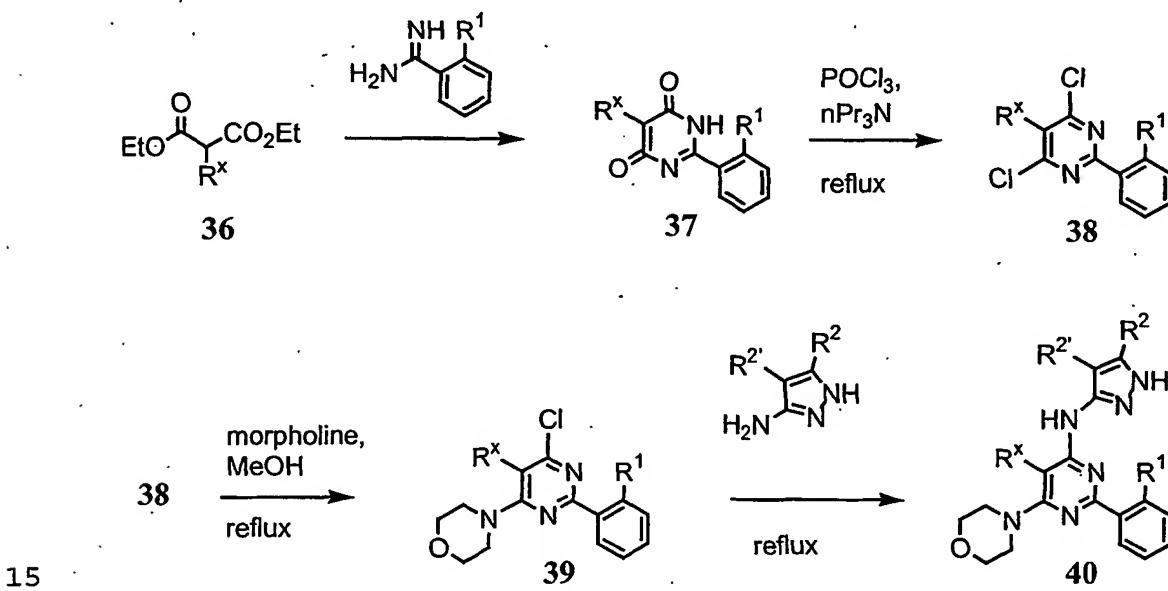
10

Methods C and D(i) above employ β -ketoesters 8 and 10, respectively, as pyrimidinone precursors. The substitution pattern of the R^x and R^y groups on the pyrimidinone ring will be reversed if a chlorocrotonate 11 (Synth. Comm., (1986), 997-1002), instead of the corresponding β -ketoester 10, is condensed with the desired benzamidine. These methods are illustrated by the following general procedure.

To a solution of a β -ketoester (5.2 mmol) and 20 amidinium chloride (5.7 mmol) in ethanol (5 mL) is added sodium ethoxide (7.8 mmol). The mixture is heated under reflux for 7-14 hours. After evaporation the resulting residue is dissolved in water, acidified with concentrated HCl to pH 6, and then filtered to obtain a 25 solid product 2-aryl-3H-pyrimidin-4-one (yield 75-87%),

which may be purified by flash column chromatography if needed. To this pyrimidinone (3.7 mmol) is added POCl_3 (4 mL) and $n\text{-Pr}_3\text{N}$ (1.4 mL). The mixture is heated under reflux for 1 hour. After evaporation of the excess POCl_3 , 5 the residue is dissolved in ethyl acetate, washed with 1N NaOH solution (three times) and NaHCO_3 (once), and dried over MgSO_4 . The solvent is removed under vacuum and the residue is purified by flash column chromatography eluting with 10% of ethyl acetate in hexanes to give 2-
10 aryl-4-chloro-pyrimidine as a pale yellow syrup. This crude product may be treated with a 3-aminopyrazole or 3-aminoindazole as described above.

Method D(ii)



Method D(ii) above shows a general route for the preparation of the present compounds, such as compound 40, wherein R^Y is $\text{N}(\text{R}^4)_2$. See *Il Farmaco*, 52(1) 20 61-65 (1997). Displacement of the 6-chloro group is exemplified here using morpholine. This method is illustrated by the following procedure.

To a solution of 2-methylmalonic acid diethyl ester (5 mmol) and sodium ethoxide (15 mmol) is added the

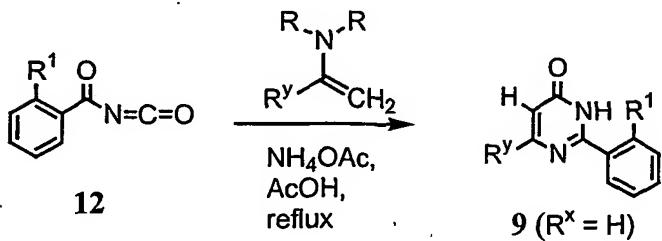
appropriate amidine salt (5 mmol) in ethanol (10 mL) and the reaction heated at reflux for 2-24 hours. The residue is dissolved in water and acidified with 2N HCl. The resulting precipitate is filtered off and further purified by flash chromatography (yield 5-35%) to afford the pyrimidinedione 37. To 37 (1.6 mmol) is added POCl₃ (32 mmol) and tri-n-propylamine (6.4 mmol) and the reaction refluxed is for 1h. After evaporation of excess POCl₃, the residue is dissolved in ethyl acetate, basified with 1N NaOH, separated and the aqueous phase twice more extracted with ethyl acetate. The combined organics are dried (sodium sulfate) and evaporated. Purification by flash chromatography provides the dichloropyrimidine (38) as a yellow oil in 23% yield.

15 A solution of 38 (0.33 mmol) in methanol (5 mL)
is treated with an amine, exemplified here using
morpholine (0.64 mmol) and refluxed 1 hour. After
evaporation of solvent, the residue is purified by flash
chromatography to provide the mono-chloropyrimidine 39 as
20 a colorless oil in 75% yield.

The mono-chloropyrimidine, 39, (0.19 mmol) may be treated with a 3-aminopyrazole or 3-aminoindazole compound in a manner substantially similar those described above in Methods A and B.

25

Method E

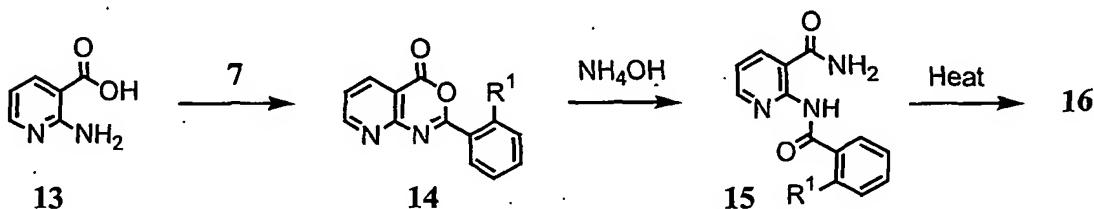


As shown by Method E, an acyl isocyanate 12 may
30 be condensed with an enamine to provide pyrimidinone 9

(J. Org. Chem. (1993), 58, 414-418; J. Med. Chem., (1992), 35, 1515-1520; J. Org. Chem., 91967, 32, 313-214). This method is illustrated by the following general procedure.

The enamine is prepared according to W. White,
 5 et al., J. Org. Chem. (1967), 32, 213-214. The acyl
 isocyanate is prepared according to G Bradley, et al, J
 Med. Chem. (1992), 35, 1515-1520. The coupling reaction
 then follows the procedure of S Kawamura, et al, J. Org.
 Chem., (1993), 58, 414-418. To the enamine (10 mmol) in
 10 tetrahydrofuran (30 mL) at 0°C under nitrogen is added
 dropwise over 5 min a solution of acyl isocyanate (10
 mmol) in tetrahydrofuran (5 mL). After stirring for 0.5
 h, acetic acid (30 mL) is added, followed by ammonium
 acetate (50 mmol). The mixture is refluxed for 2 h with
 15 continuous removal of tetrahydrofuran. The reaction is
 cooled to room temperature and is poured into water (100
 mL). The precipitate is filtered, washed with water and
 ether and dried to provide the 2-aryl-3H-pyrimidin-4-one.

20 Method F



Method F shows a general route for the preparation of the present compounds wherein R^X and R^Y are taken together to form a 5-8 membered partially unsaturated saturated or unsaturated ring having 1-3 heteroatoms. The condensation of a 2-amino-carboxylic acid, such as 2-amino-nicotinic acid 13, and an acid chloride 7 provides an oxazinone 14. Treatment of 14 with ammonium hydroxide will furnish the benzamide 15

which may be cyclized to a 2-(substituted)-pyrido[2,3-d][1,3]pyrimidin-4-one 16. This method is illustrated by the following procedure.

2-(Trifluoromethyl)benzoyl chloride (4.2 ml, 5 29.2 mmol) is added dropwise to a solution of 2-aminonicotinic acid (2.04g, 14.76 mmol) in 20 ml of pyridine. The reaction mixture is heated at 158 C for 30 min then cooled to room temperature. The reaction is poured into 200 ml of water and an oil forms which 10 solidifies upon stirring. The solid is collected by vacuum filtration and washed with water and diethyl ether. The product is dried to give 2-(2-trifluoromethyl-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (2.56 g, 60% yield) which may be used in the next step 15 without further purification.

2-(2-Trifluoromethyl-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (2.51g) is stirred in 30% ammonium hydroxide (25 ml) at room temperature overnight. The resulting precipitate is filtered and rinsed with water 20 and diethyl ether. The precipitate is dried under vacuum at 50 C overnight to give 2-(2-trifluoromethyl-benzoylamino)-nicotinamide (850 mg, 33% yield)

2-(2-Trifluoromethyl-benzoylamino)-nicotinamide (800mg, 2.6mmol) is dissolved in 10ml of ethanol. 25 Potassium ethoxide (435mg, 5.2mmol) is added to the solution which is heated to reflux for 16 h. The reaction mixture is evaporated in vacuo to afford a gummy residue that is dissolved in water and acidified with 10% sodium hydrogen sulfate to pH 7. The resulting 30 precipitate is filtered and dried under vacuum at 50 C to give 2-(2-trifluoromethyl-phenyl)-3H-pyrido[2,3-d]pyrimidin-4-one.

Method G

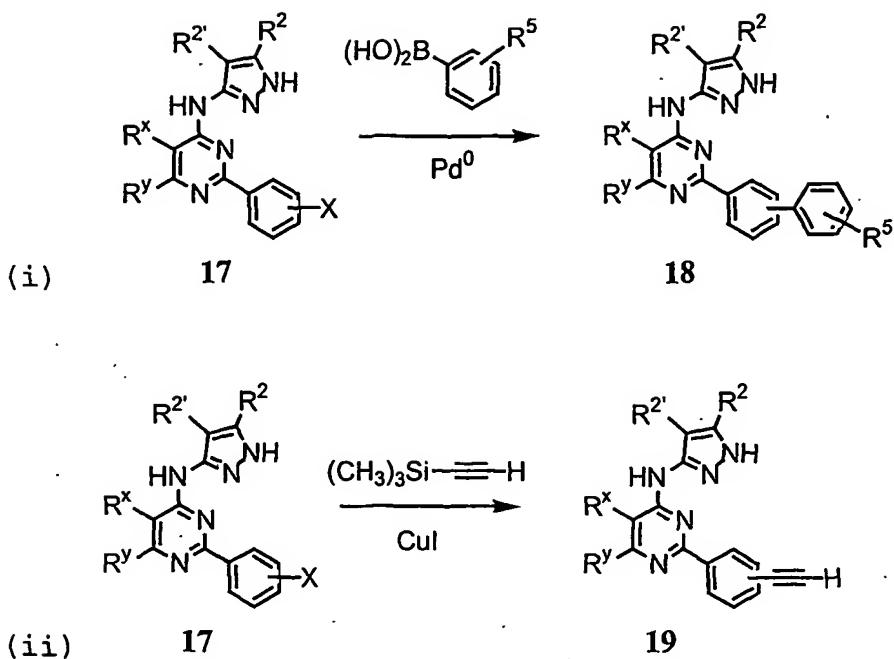
Method G is analogous to Method B(i) above. This method is illustrated by the following general procedure.

5 2-(3,4-Dichloro-phenyl)-3H-quinazolin-4-one (1g, 3.43 mmol) is suspended in phosphorus oxychloride (4 mL) and the reaction mixture was stirred at 110°C for 3 hours. The solvents are then evaporated and the residue is treated carefully with an ice cold aqueous saturated
10 solution of NaHCO₃. The solid is collected by filtration and washed with ether to give 4-chloro-2-(3,5-dichloro-phenyl)-quinazoline as a white solid (993 mg, 93%).

To 4-chloro-2-(3,5-dichloro-phenyl)-quinazoline (4.00mg, 1.29 mmol) in THF (30 mL) is added 3-amino-5-methyl pyrazole (396 mg, 2.58 mmol) and the reaction mixture is heated at 65°C overnight. The solvents are then evaporated and the residue triturated with ethyl acetate, filtered and washed with a minimum amount of ethanol to give [2-(3,4-dichlorophenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine as a white solid (311 mg 65%): mp 274°C; ¹H NMR (DMSO) δ 2.34 (3H, s), 6.69 (1H, s), 7.60 (1H, m), 7.84 (1H, d), 7.96 (2H, d), 8.39 (1H, dd), 8.60 (1H, d), 8.65 (1H, d), 10.51 (1H, s), 12.30 (1H, s); IR (solid) 1619, 1600, 1559, 1528, 1476, 1449, 25 1376, 1352, 797, 764, 738; MS 370.5 (M+H)⁺.

The THF solvent used in the previous step may be replaced by other organic solvents such as ethanol, N,N-dimethylformamide, or dioxane.

30 Method H



5 Method H shows routes in which a Ring D aryl group bearing a halogen (X is Br or I) may be converted to other formula III compounds. Method H(i) shows a phenylboronic acid coupling to Ring D to provide compound 18 and Method H(ii) shows an acetylene coupling to provide compound 19. Substituent X in compound 17 may be bromine or iodine. These methods are illustrated by the following procedures.

10 15 20

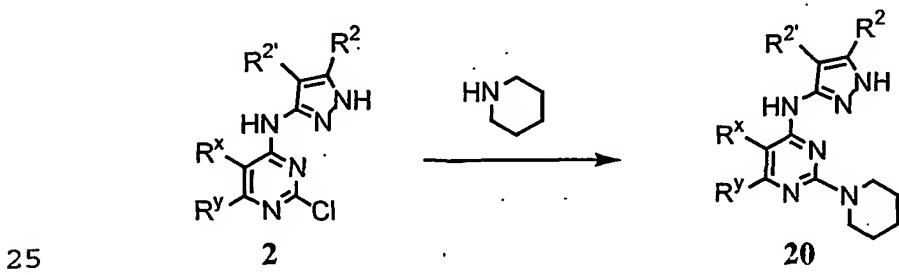
Method H(i). To a mixture of [2-(4-bromo-phenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (196 mg, 0.51 mmol) and phenylboronic acid (75 mg, 0.62 mmol) in THF/water (1/1, 4 mL) is added Na₂CO₃ (219 mg, 2.06 mmol), triphenylphosphine (9mg, 1/15 mol%) and palladium acetate (1 mg, 1/135 mol%). The mixture is heated at 80°C overnight, the solvents are evaporated and the residue is purified by flash chromatography (gradient of CH₂Cl₂/MeOH) to give (2-biphenyl-4-yl-quinazolin-4-yl)-(5-methyl-2H-pyrazol-3-yl)-amine as a yellow solid (99 mg, 51%): ¹H NMR (DMSO) δ 2.37 (3H, s), 6.82 (1H, s), 7.39-

7.57 (4H, m), 7.73-7.87 (6H, m), 8.57 (2H, d), 8.67 (1H, d), 10.42 (1H, s), 12.27 (1H, s); MS 378.2 ($M+H$)⁺

Method H(ii). To a mixture of [2-(4-bromo-phenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (114 mg, 0.3 mmol), and trimethylsilylacetylene (147 mg, 1.5 mmol) in DMF (2 mL) is added CuI (1.1 mg, 1/50 mol%), Pd(PPh₃)₂Cl₂ (4.2 mg, 1/50 mol%) and triethylamine (121 mg, 0.36 mmol). The mixture is heated at 120°C overnight and the solvent is evaporated. The residue is triturated in ethyl acetate and the precipitate is collected by filtration.

To the above precipitate suspended in THF (3 mL) is added tetrabutylammonium fluoride (1M in THF, 1.1eq). The reaction mixture is stirred at room temperature for two hours and the solvent is evaporated. The residue is purified by flash chromatography (gradient of CH₂Cl₂/MeOH) to give [2-(4-ethynylphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine as a white solid (68 mg, 70%): ¹H NMR (DMSO) δ 2.34 (3H, s), 4.36 (1H, s), 6.74 (1H, s), 7.55 (1H, m), 7.65 (2H, d), 7.84 (2H, m), 8.47 (2H, d), 8.65 (1H, d), 10.43 (1H, s), 12.24 (1H, s); MS 326.1 (M+H)⁺

Method I

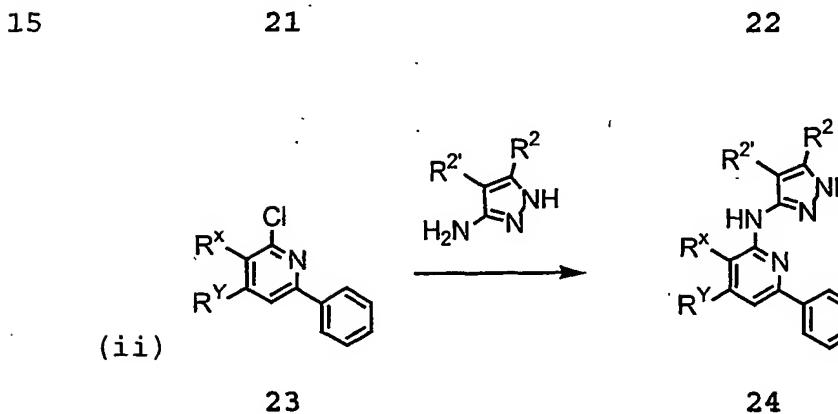
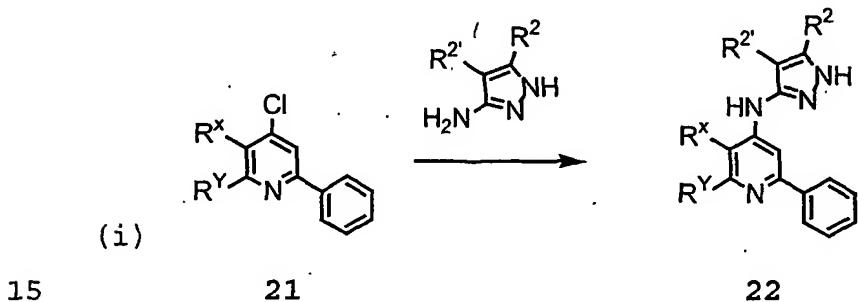


Method I above shows a general route for the preparation of the present compounds wherein ring D is a heteroaryl or heterocyclyl ring directly attached to the

pyrimidine 2-position via a nitrogen atom. Displacement of the 2-chloro group, exemplified here using piperidine, may be carried out in a manner similar to that described in *J. Med. Chem.*, 38, 2763-2773 (1995) and *J. Chem. Soc.*, 5 1766-1771 (1948). This method is illustrated by the following procedure.

To a solution of (2-chloro-quinazolin-4-yl)-(1*H*-indazol-3-yl)-amine (1 equivalent, 0.1-0.2 mmol) in N, N-dimethylacetamide (1 ml) is added the desired amine 10 (3 equivalents). The resulting mixture is maintained at 100°C for 6 h and then purified by reverse-phase HPLC.

Method J



20 Method J above shows the preparation of compounds of formula V via the displacement of a chloro group from an appropriately substituted pyridyl ring. Method J(i) is a route for preparing compounds of formula Va (see *Indian J. Chem. Sect.B*, 35, 8, 1996, 871-873). 25 Method J(ii) is a route for preparing compounds of

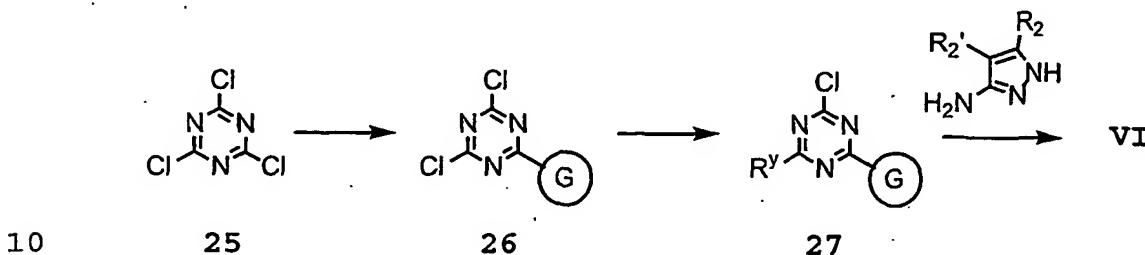
formula Vb (see *Bioorg. Med. Chem.*, 6, 12, 1998, 2449-2458). For convenience, the chloropyridines 21 and 23 are shown with a phenyl substituent corresponding to Ring D of formula V. It would be apparent to one skilled in the art that Method J is also useful for preparing compounds of formula V wherein Ring D is heteroaryl, heterocyclyl, carbocyclyl or other aryl rings. Method J is illustrated by the following procedures.

Method J(i). (5-Methyl-2H-pyrazol-3-yl)-(2-phenyl-quinolin-4-yl)-amine. To 4-chloro-2-phenylquinoline (*J. Het. Chem.*, 20, 1983, 121-128) (0.53g, 2.21 mmol) in diphenylether (5 mL) was added 3-amino-5-methylpyrazole (0.43g, 4.42 mmol) and the mixture was heated at 200°C overnight with stirring. To the cooled mixture was added petroleum ether (20 mL) and the resulting crude precipitate was filtered and further washed with petroleum ether. The crude solid was purified by flash chromatography (SiO₂, gradient DCM-MeOH) to give the title compound as a white solid: mp 242-244°C; ¹H NMR (DMSO) δ 2.27(3H, s), 6.02(1H, s), 7.47(2H, d), 7.53-7.40(2H, br m), 7.67(1H, m), 7.92(1H, m), 8.09(2H, d), 8.48(2H, m), 9.20(1H, s), 12.17(1H, br s); IR (solid) 1584, 1559, 1554, 1483, 1447, 1430, 1389; MS 301.2 (M+H)⁺

Method J(ii). (5-Methyl-2H-pyrazol-3-yl)-(3-phenyl-isquinolin-1-yl)-amine. To 1-chloro-3-phenylisoquinoline (*J. Het. Chem.*, 20, 1983, 121-128) (0.33g, 1.37 mmol) in dry DMF (5 mL) was added 3-amino-5-methylpyrazole (0.27g, 2.74 mmol) and potassium carbonate (0.57g, 4.13 mmol) and the mixture was heated under reflux for 6 hours. The mixture was cooled and the bulk of DMF was evaporated. The residue was extracted twice with ethyl acetate and the combined organic layers were washed with brine, dried (MgSO₄), filtered and

concentrated. The crude was purified by flash chromatography (SiO_2 , gradient DCM-MeOH) to give the title compound as a colourless oil; ^1H NMR (MeOD) δ 2.23 (3H, s), 5.61 (1H, s), 7.41 (1H, m), 7.52 (2H, m), 7.62 (1H, m), 7.81 (1H, m), 8.07 (1H, d), 8.19 (2H, m), 8.29 (1H, s), 8.54 (1H, d); MS 301.2 ($\text{M}+\text{H}$)⁺

Method K

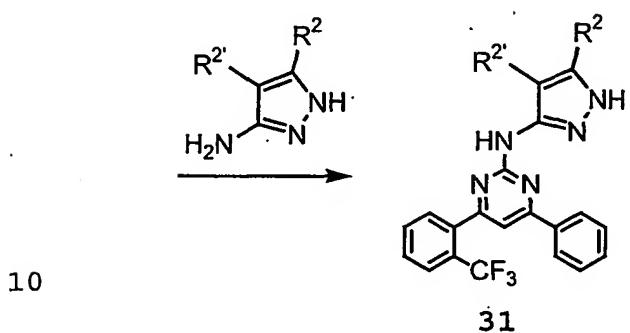
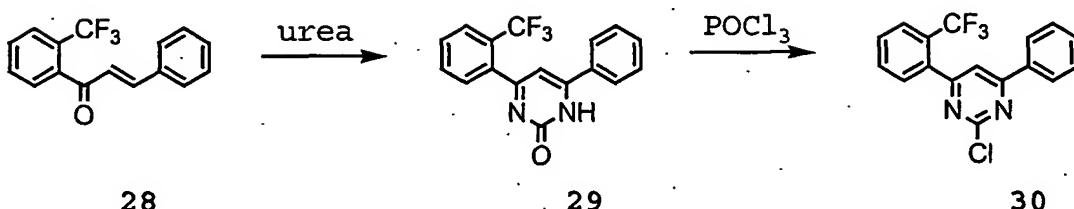


Method K shows a route for the preparation of compounds of formula VI. A versatile starting material is 2,4,6-trichloro-[1,3,5]triazine 25 in which the chlorine substituents may be sequentially displaced. The displacement of one of the chlorines by an aryl Grignard reagent or an aryl boronic acid is described in PCT patent application WO 01/25220 and *Helv. Chim. Acta*, 33, 1365 (1950). The displacement of one of the chlorines by a heteroaryl ring is described in WO 01/25220; *J. Het. Chem.*, 11, 417 (1974); and *Tetrahedron* 31, 1879 (1975). These reactions provide a 2,4-dichloro-(6-substituted) [1,3,5]triazine 26 that is a useful intermediate for the preparation of compounds of formula VI. Alternatively, intermediate 26 may be obtained by constructing the triazine ring by known methods. See US patent 2,832,779; and US patent 2,691020 together with *J. Am. Chem. Soc.* 60, 1656 (1938). In turn, one of the chlorines of 26 may be displaced as described above to provide 2-chloro-(4,6-disubstituted) [1,3,5]triazine 27.

The treatment of 27 with an appropriate aminopyrazole provides the desired compound of formula VI.

Method L

5

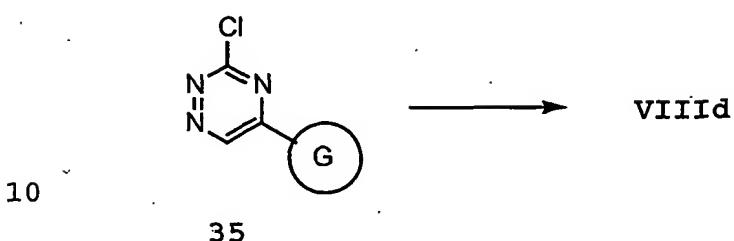
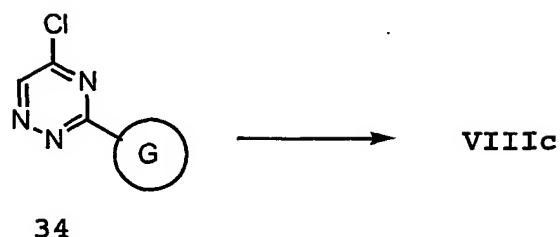
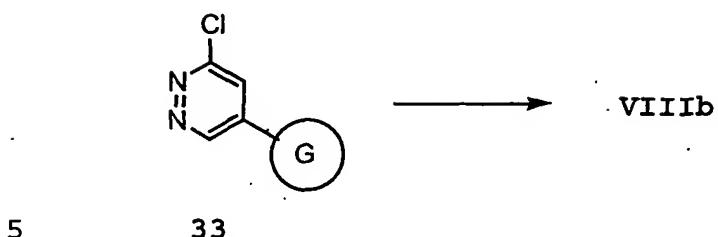
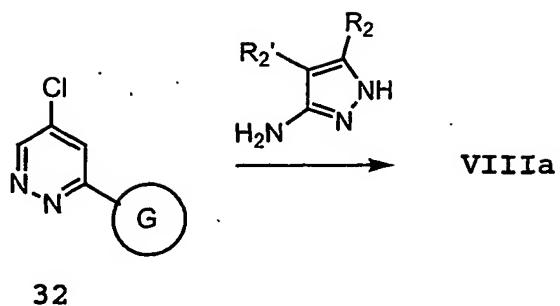


Method L shows a route for preparing compounds of formula VII. For illustration purposes the 15 trifluoromethylchalcone 28 is used as a starting material; however, it would be apparent to one skilled in the art that other rings may be used in place of the trifluoromethylphenyl and phenyl rings of compound 28. Substituted chalcones may be prepared by known methods, 20 for example as described in the *Indian J. Chemistry*, 32B, 449 (1993). Condensation of a chalcone with urea provides the pyrimidinone 29, which may be treated with POCl₃ to give the chloropyrimidine 30. See *J. Chem. Eng. Data*, 30(4) 512 (1985) and *Egypt. J. Chem.*, 37(3), 283.

(1994). In an alternative approach to compound 30, one of the aryl rings attached to the pyrimidine is introduced by displacement of the 4-chloro group of 2,4-dichloro-(6-aryl)-pyrimidine by an aryl boronic acid 5 using a palladium catalyst such as $(Ph_3P)_4Pd$ in the presence of a base such as sodium carbonate as described in *Bioorg. Med. Lett.*, 9(7), 1057 (1999).. Displacement of the chlorine of compound 30 by an appropriate aminopyrazole provides compounds of this invention, such 10 as 31. The last step of this method is illustrated by the following procedure.

[4-(4-Methylpiperidin-1-yl)-pyrimidin-2-yl]-(5-methyl-2H-pyrazol-3-yl)-amine. To a solution of 2-chloro-4-(4-methylpiperidin-1-yl)-pyrimidine (prepared 15 using a procedure similar to the one reported in *Eur. J. Med. Chem.*, 26(7) 729(1991)) (222 mg, 1.05 mmol) in BuOH (5 mL) was added 3-amino-5-methyl-2H-pyrazole (305mg, 3.15 mmol) and the reaction mixture was then heated under reflux overnight. The solvent was evaporated and the 20 residue dissolved in a mixture ethanol/water (1/3, 4 mL). Potassium carbonate (57mg, 0.41 mmol) was added and the mixture was stirred at room temperature for 2 hours. The resulting suspension was filtered, washed with water twice and rinsed with ether twice to give the title. 25 compound as a white solid (143mg, 50%): mp 193-195°C; 1H NMR (DMSO) δ 0.91 (3H, d), 1.04 (2H, m), 1.67 (3H, m), 2.16 (3H, s), 2.83 (2H, t), 4.31 (2H, m), 6.19 (2H, m), 7.87 (1H, d), 8.80 (1H, br s), 11.71 (1H, s); IR (solid) 1627, 1579, 1541, 1498, 1417, 1388, 1322, 1246; MS 30 273.3 ($M+H$)⁺.

Method M

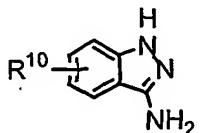


Method M provides routes for obtaining compounds of formula **VIII**. A general procedure for displacing the chlorine of a 4-chloro-6-substituted-pyridazine, **32**, with an appropriately substituted pyrazole to provide **VIIIA** is described in *J. Het. Chem.*, 20, 1473 (1983). Analogous reactions may be carried out as follows: (a) with 3-chloro-5-substituted-pyridazine, **33**, to provide **VIIIB** is described in *J. Med. Chem.*, 41(3), 311 (1998); (b) with 5-chloro-3-substituted-

[1,2,4]triazine, 34, to provide VIIId is described in *Heterocycles*, 26(12), 3259 (1987); and (c) with 3-chloro-5-substituted-[1,2,4]triazine, 35, to provide VIIId is described in *Pol. J. Chem.*, 57, 7, (1983); *Indian J. Chem. Sect. B*, 26, 496 (1987); and *Agric. Biol. Chem.*, 54(12), 3367 (1990). An alternative procedure to compounds of formula VIIId is described in *Indian J. Chem. Sect. B*, 29(5), 435 (1990).

Compounds of formula IX are prepared by methods substantially similar to those described above for the pyrazole-containing compounds of formula I. Methods A-J may be used to prepare the triazole-containing compounds of formula IX by replacing the amino-pyrazole compound with an amino-triazole compound. Such methods are specifically exemplified by Synthetic Examples 415-422 set forth below. The amino-triazole intermediate may be obtained by methods described in *J. Org. Chem. USSR*, 27, 952-957 (1991).

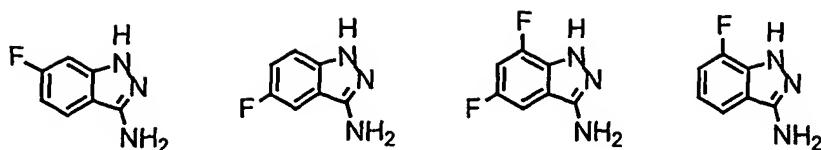
Certain synthetic intermediates that are useful for preparing the protein kinase inhibitors of this invention are new. Accordingly, another aspect of this invention relates to a 3-aminoindazole compound of formula A:



A

25

where R¹⁰ is one to three substituents that are each independently selected from fluoro, bromo, C₁₋₆ haloalkyl, nitro, or 1-pyrrolyl. Examples of such compounds include the following:

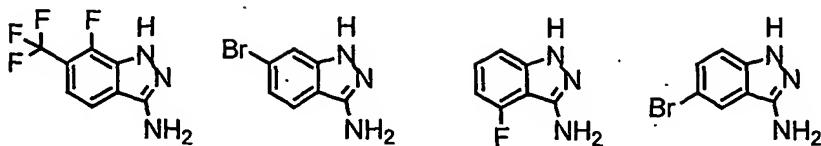


A1

A2

A3

A4



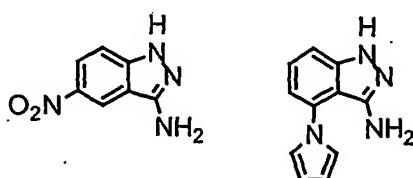
5

A5

A6

A7

A8

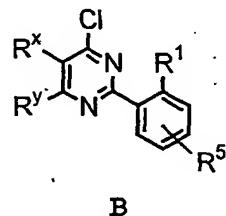


A9

A10

Another aspect of this invention relates to a

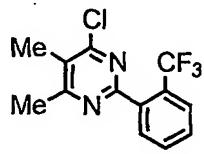
10 4-chloropyrimidine compound of formula B:



B

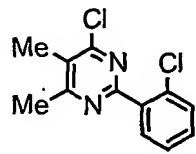
wherein R^x and R^y are as defined above; R¹ is selected from Cl, F, CF₃, CN, or NO₂; and is one to three

15 substituents that are each independently selected from H, Cl, F, CF₃, NO₂, or CN; provided that R¹ and R⁵ are not simultaneously Cl. Examples of compounds of formula B are shown below:

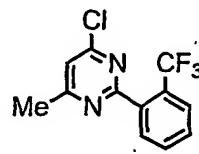


20

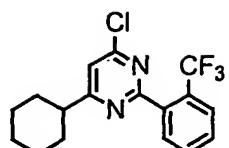
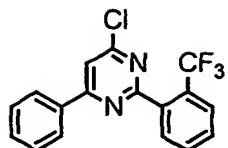
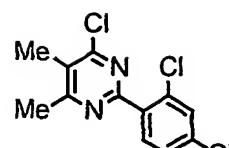
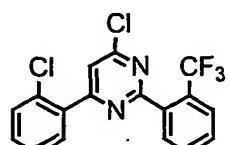
B1



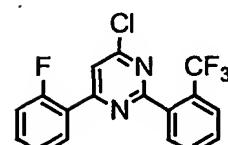
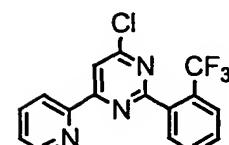
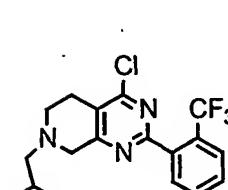
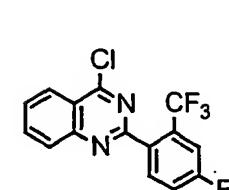
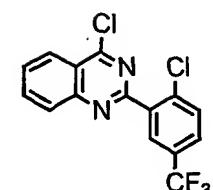
B2



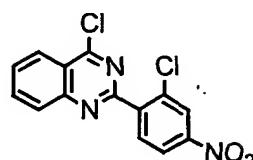
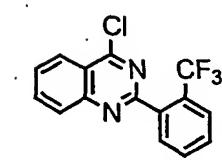
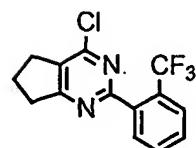
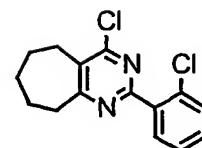
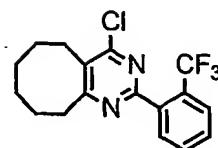
B3

**B4****B5****B6**

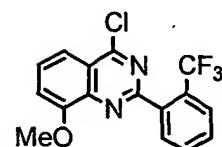
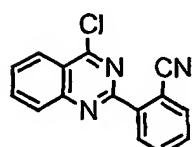
5

B7**B8****B9****B10****B11****B12**

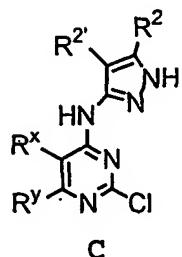
10

B13**B14****B15****B16****B17****B18**

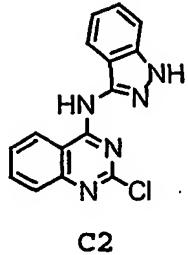
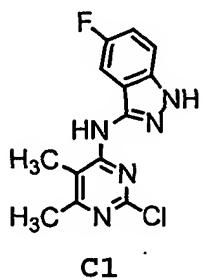
15

**B19****B20**

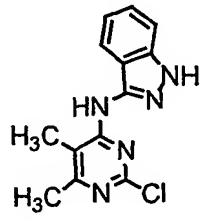
Another aspect of this invention relates to compounds of formula C:



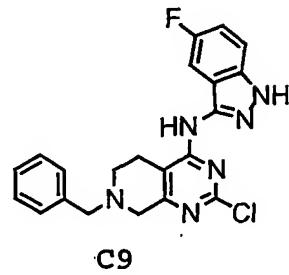
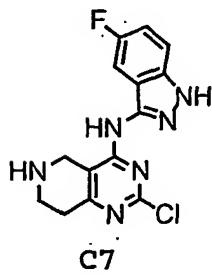
5 wherein R^x , R^y , R^2 , and $R^{2'}$ are as defined above. Examples of compounds of formula C are shown below:

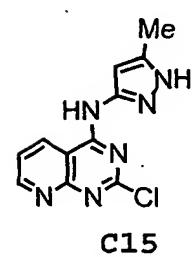
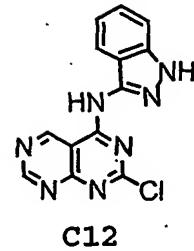
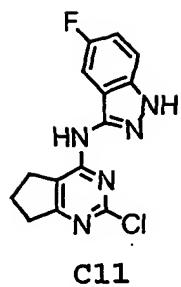
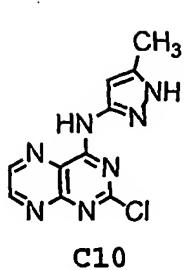


10

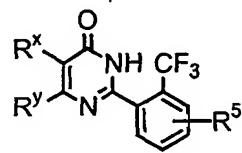


15





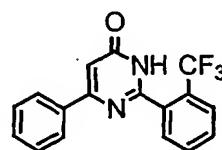
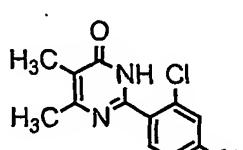
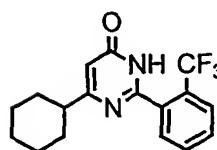
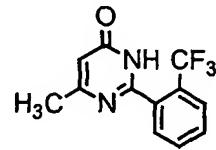
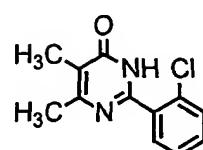
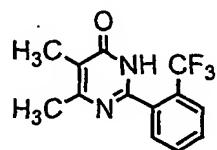
Yet another aspect of this invention relates to compounds of formula D:



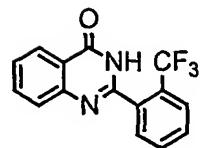
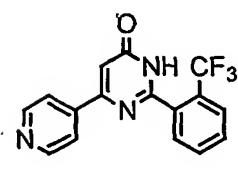
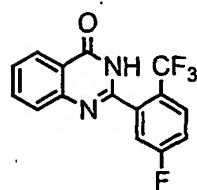
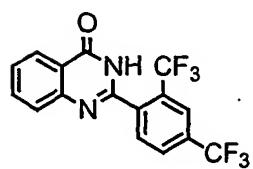
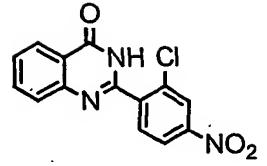
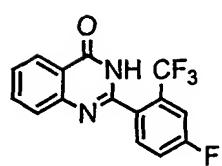
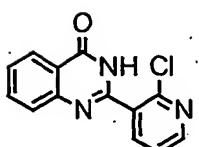
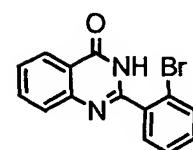
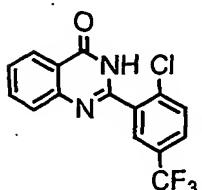
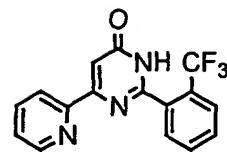
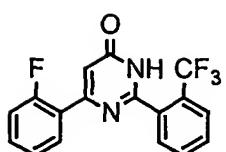
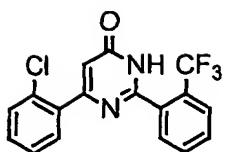
10

where R^5 , R^x and R^y are as defined above. Examples of formula D compounds and other useful pyrimidinone intermediates are shown below:

15



20



In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

SYNTHETIC EXAMPLES

The following HPLC methods were used in the analysis of the compounds as specified in the Synthetic Examples set forth below. As used herein, the term "R_t" refers to the retention time observed for the compound using the HPLC method specified.

HPLC-Method A:

10 Column: C18, 3 um, 2.1 X 50 mm, "Lighting" by Jones Chromatography.
Gradient: 100% water (containing 1% acetonitrile, 0.1% TFA) to 100% acetonitrile (containing 0.1% TFA) over 4.0 min, hold at 100% acetonitrile for 1.4 min
15 and return to initial conditions. Total run time 7.0 min. Flow rate: 0.8 mL/min.

HPLC-Method B:

Column: C18, 5 um, 4.6 X 150 mm "Dynamax" by Rainin
20 Gradient: 100% water (containing 1% acetonitrile, 0.1% TFA) to 100% acetonitrile (containing 0.1% TFA) over 20 min, hold at 100% acetonitrile for 7.0 min and return to initial conditions. Total run time 31.5 min. Flow rate: 1.0 mL/min.

25

HPLC-Method C:

Column: Cyano, 5 um, 4.6 X 150 mm "Microsorb" by Varian.
Gradient: 99% water (0.1% TFA); 1% acetonitrile (containing 0.1% TFA) to 50% water (0.1% TFA), 50% acetonitrile (containing 0.1% TFA) over 20 min, hold for 8.0 min and return to initial conditions. Total run time 30 min. Flow rate: 1.0 mL/min.

HPLC-Method D:

Column: Waters (YMC) ODS-AQ 2.0x50mm, S5, 120A.

Gradient: 90% water (0.2% Formic acid), 10%
5 acetonitrile (containing 0.1% Formic acid) to 10%
water (0.1% formic acid), 90% acetonitrile
(containing 0.1% formic acid) over 5.0 min, hold for
0.8 min and return to initial conditions. Total run
time 7.0 min.

10 Flow rate: 1.0 mL/min.

HPLC-Method E:

Column: 50x2.0mm Hypersil C18 BDS; 5 μ m

Gradient: elution 100% water (0.1% TFA), to 5% water
15 (0.1% TFA), 95% acetonitrile (containing 0.1% TFA)
over 2.1 min, returning to initial conditions after
2.3 min.

Flow rate: 1 mL/min.

20 Example 1 [2-(2-Chlorophenyl)-5,6-dimethylpyrimidin-4-yl]-
(5-Methyl-2H-pyrazol-3-yl)-amine (II-1): 1 HNMR (500 MHz,
DMSO-d6) δ 10.4 (s, br, 1H), 7.74 (m, 2H), 7.68 (m, 1H),
7.60 (m, 1H), 6.39 (s, 1H), 2.52 (s, 3H), 2.30 (s, 3H),
2.22 (s, 3H); MS 314.1 (M+H).

25 Example 2 [2-(2-Chloro-phenyl)-6,7,8,9-tetrahydro-5H-
cycloheptapyrimidin-4-yl]-(1H-indazol-3-yl)-amine (II-2):
Prepared in 30% yield. 1 HNMR (500MHz, DMSO-d6) δ 1.72 (m,
4H), 1.91 (m, 2H), 3.02 (m, 4H), 7.05 (t, 1H), 7.33 (t,
30 1H), 7.39 (m, 1H), 7.47 (d, 1H), 7.55 (m, 3H), 7.59 (d,
1H), 10.4 (m, 1H), 13.11 (br. s, 1H); EI-MS 390.2 (M+H);
HPLC-Method A, R_t 2.99 min.

Example 3 (5-Fluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl]-amine (II-3): Compound II-18 (90 mg, 0.17 mmol) was treated with an equal weight of Pd/C (10%) in 4.4% formic acid in MeOH at room temperature for 14 h. The mixture was filtered through celite, the filtrate was evaporated, and crude product was purified by HPLC to provide 18 mg (24%) of the desired product as pale yellow solid. ^1H NMR (500 MHz, DMSO-d6) δ 12.9 (s, 1H), 9.51 (s, 1H), 9.26 (s, 2H), 7.72 (d, 1H), 7.63 (t, 1H), 7.58 (t, 1H), 7.49 (m, 2H), 7.21 (td, 1H), 7.15 (dd, 1H), 4.24 (s, 2H), 3.56 (m, 2H), 2.95 (m, 2H) ppm. MS (ES+): m/e= 429.22 (M+H); HPLC-Method A, R_t 2.88 min.

Example 4 [2-(2-Chloro-phenyl)-6,7,8,9-tetrahydro-5*H*-cycloheptapyrimidin-4-yl]- (7-fluoro-1*H*-indazol-3-yl)-amine (II-4): Prepared in 52% yield to afford a white solid. ^1H NMR (500MHz, DMSO-d6) δ 1.72 (m, 4H), 1.92 (m, 2H), 3.00 (m, 4H), 7.02 (td, 1H), 7.20 (dd, 1H), 7.40 (m, 1H), 7.42 (d, 1H), 7.52 (m, 3H), 10.5 (m, 1H), 13.50 (br. s, 1H); EI-MS 408.2 (M+H); HPLC-Method A, R_t 3.00 min.

Example 5 [2-(2-Chloro-phenyl)-6,7,8,9-tetrahydro-5*H*-cycloheptapyrimidin-4-yl]- (5-fluoro-1*H*-indazol-3-yl)-amine (II-5): Prepared in 51% yield. ^1H NMR (500MHz, DMSO-d6) δ 1.71 (m, 4H), 1.91 (m, 2H), 3.01 (m, 4H), 7.24 (td, 1H), 7.41 (m, 2H), 7.54 (m, 4H), 10.5 (m, 1H), 13.1 (br. s, 1H); EI-MS 408.2 (M+H); HPLC-Method A, R_t 3.05 min.

Example 6 [2-(2-Chloro-phenyl)-6,7,8,9-tetrahydro-5*H*-cycloheptapyrimidin-4-yl]- (5,7-difluoro-1*H*-indazol-3-yl)-amine (II-6): Prepared according to Method C in 72% yield. ^1H NMR (500MHz, DMSO-d6) δ 1.72 (m, 4H), 1.91 (m,

2H), 3.01 (m, 4H), 7.31 (m, 2H), 7.41 (m, 1H), 7.54 (m, 3H), 10.5 (m, 1H), 13.6 (br. s, 1H); EI-MS 426.2 (M+H); HPLC-Method A, R_t 3.21 min.

5 Example 7 (7-Fluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydroquinazolin-4-yl]-amine (II-7): Prepared in 62% yield. ¹HNMR (500 MHz, DMSO-d6) δ 13.5 (s, br, 1H), 10.1 (s, br, 1H), 7.75 (m, 4H), 7.33 (d, 1H), 7.17 (dd, 1H), 7.00 (td, 1H), 2.80 (m, 2H), 2.71 (m, 2H), 1.89 (br, 4H) ppm; LC-MS (ES+) 428.44 (M+H), (ES-) 426.43 (M-H); HPLC-Method A, R_t 3.02 min.

10 Example 8 (5-Fluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydroquinazolin-4-yl]-amine (II-8): Prepared in 53% yield. ¹HNMR (500 MHz, DMSO-d6) δ 13.1 (s, 1H), 10.2 (s, br, 1H), 7.75 (m, 4H), 7.50 (dd, 1H), 7.27 (dd, 1H), 7.21 (td, 1H), 2.80 (m, 2H), 2.72 (m, 2H), 1.88 (m, 4H) ppm; MS (ES+) 428.43 (M+H), (ES-) 426.43 (M-H); HPLC-Method A, R_t 3.01 min.

20 Example 9 (5,7-Difluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydroquinazolin-4-yl]-amine (II-9): Prepared in 37% yield. ¹HNMR (500 MHz, DMSO-d6) δ 13.7 (s, 1H), 10.2 (s, br, 1H), 7.80 (d, 1H), 7.76 (t, 1H), 7.69 (m, 2H), 7.31 (t, 1H), 7.18 (d, 1H), 2.81 (t, br, 2H), 2.72 (t, br, 2H), 1.90 (m, 4H) ppm; MS (ES+) 446.42 (M+H), (ES-) 444.37 (M-H); HPLC-Method A, R_t 3.09 min.

30 Example 10 (5-Trifluoromethyl-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydroquinazolin-4-yl]-amine (II-10): Prepared by Method C in ethanol in 35% yield. ¹HNMR (500 MHz, DMSO-d6) δ 13.2 (s, 1H), 10.1

(s, br, 1H), 8.01 (s, 1H), 7.76 (d, 1H), 7.66 (m, 4H), 7.57 (d, 1H), 2.79 (m, 2H), 2.73 (m, 2H), 1.89 (m, 4H) ppm. MS (ES+) 478.45 (M+H), (ES-) 476.42 (M-H); HPLC-Method A, R_t 3.21 min.

5

Example 11 (5,7-difluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-6,7,8,9-tetrahydro-5*H*-cycloheptapyrimidin-4-yl]-amine (II-11): Prepared in 60% yield. White solid. ¹HNMR (500MHz, DMSO-d6) δ 1.72 (m, 4H), 1.91 (m, 2H), 3.01 (m, 4H), 7.15 (dd, 1H), 7.30 (td, 1H), 7.66 (m, 2H), 7.72 (t, 1H), 7.78 (d, 1H), 10.2 (m, 1H), 13.5 (br. s, 1H); EI-MS 460.2 (M+H); HPLC-Method A, R_t 3.13 min.

15 Example 12 (6-Benzyl-2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yl)-(5-fluoro-1*H*-indazol-3-yl)-amine (II-12): Prepared in 49% yield. ¹HNMR (500 MHz, DMSO-d6) δ 12.8 (s, 1H), 9.11 (s, 1H), 7.68 (d, 1H), 7.58 (t, 1H), 7.53 (t, 1H), 7.44 (m, 4H), 7.37 (t, 2H), 7.29 (t, 1H), 7.19 (m, 2H), 3.78 (s, 2H), 3.61 (s, 2H), 2.81 (s, br, 4H) ppm; LC-MS (ES+) 519.24 (M+H); HPLC-Method A, R_t 3.11 min.

25 Example 13 (1*H*-Indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-6,7,8,9-tetrahydro-5*H*-cycloheptapyrimidin-4-yl]-amine (II-13): Prepared in 40% yield. ¹HNMR (500MHz, DMSO-d6) δ 1.70 (m, 4H), 1.90 (m, 2H), 3.00 (m, 4H), 7.01 (t, 1H), 7.30 (td, 1H), 7.44 (d, 1H), 7.49 (d, 1H), 7.68 (m, 3H), 7.77 (d, 1H), 10.01 (m, 1H), 12.83 (s, 1H); EI-MS 424.2 (M+H); HPLC-Method A, R_t 3.17 min.

30 Example 14 (7-Fluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-6,7,8,9-tetrahydro-5*H*-

cycloheptapyrimidin-4-yl]-amine (II-14): Prepared in 78% yield. ^1H NMR (500MHz, DMSO-d6) δ 1.71 (m, 4H), 1.91 (m, 2H), 3.00 (m, 4H), 6.98 (td, 1H), 7.16 (dd, 1H), 7.31 (d, 1H), 7.68 (m, 3H), 7.77 (d, 1H), 10.25 (m, 1H), 13.40 (br. s, 1H); EI-MS 442.2 (M+H); HPLC-Method A, R_t 3.12 min.

Example 15 (5-Fluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-6,7,8,9-tetrahydro-5*H*-cycloheptapyrimidin-4-yl]-amine (II-15): Prepared in 63% yield. ^1H NMR (500MHz, DMSO-d6) δ 1.71 (m, 4H), 1.91 (m, 2H), 3.00 (m, 4H), 7.20 (td, 1H), 7.25 (dd, 1H), 7.49 (dd, 1H), 7.69 (br. t, 2H), 7.74 (m, 1H), 7.79 (d, 1H), 10.35 (m, 1H), 13.00 (br. s, 1H); EI-MS 442.2 (M+H); HPLC-Method A, R_t 3.21 min.

Example 16 (5-Fluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yl]-amine (II-16): A solution of compound II-12 (45mg, 0.087 mmol) in methanol (4.4% HCOOH) was treated with an equal weight of Pd/C (10%) at room temperature for 14 h. The mixture was filtered through celite, the filtrate evaporated, and the crude product was purified by preparative HPLC to provide 15 mg (41%) of the desired product as yellow solid. ^1H NMR (500 MHz, DMSO-d6) δ 12.9 (s, 1H), 9.52 (s, 1H), 9.32 (s, 2H, TFA-OH), 7.72 (d, 1H), 7.59 (m, 2H), 7.49 (m, 2H), 7.21 (m, 1H), 7.15 (m, 1H), 4.31 (s, 2H), 3.55 (s, 2H), 3.00 (m, 2H) ppm; LC-MS (ES+) 429.20 (M+H); HPLC-Method A, R_t 2.79 min.

Example 17 (1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydroquinazolin-4-yl]-amine (II-17):

Prepared in 58% yield. ^1H NMR (500 MHz, DMSO-d6) δ 13.0 (s, 1H), 10.3 (s, br, 1H), 7.74 (m, 4H), 7.51 (d, 1H), 7.47 (d, 1H), 7.32 (t, 1H), 7.03 (t, 1H), 2.82 (m, 2H), 2.73 (m, 2H), 1.90 (m, 4H) ppm; LC-MS (ES+) 410.21 (M+H);
5 HPLC-Method A, R_t 2.99 min.

Example 18 (7-Benzyl-2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yl)-(5-fluoro-1H-indazol-3-yl)-amine (II-18): Prepared from compound B11 in 92% yield. ^1H NMR (500 MHz, DMSO-d6) δ 12.9 (s, 1H), 10.5 (s, br, 1H), 9.58 (s, 1H, TFA-OH), 7.71 (d, 1H), 7.52 (m, 9H), 7.19 (m, 2H), 4.57 (s, 2H), 4.20 (m, 2H), 3.70 (m, 2H), 3.00 (m, 2H) ppm; LC-MS (ES+) 519.23 (M+H); HPLC-Method A, R_t 3.23 min.

Example 19 (1H-Indazol-3-yl)-[6-methyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine (II-19): Prepared in 42% yield. Melting point 235-237°C; ^1H NMR (500 MHz, DMSO) δ 2.44 (3H, s), 7.09 (1H, $J=7.5$ Hz, t), 7.40 (1H, $J=7.1$ Hz, t), 7.49 (1H, $J=8.3$ Hz, d), 7.70 (3H, m), 7.79 (1H, $J=7.3$ Hz, t), 7.87 (1H, $J=8.3$ Hz, d), 8.03 (1H, $J=7.7$ Hz, d), 10.3 (1H, s), 12.6 (1H, s) ppm; HPLC-Method A, R_t 2.958 min; MS (FIA) 370.2 (M+H)⁺.

Example 20 (1H-Indazol-3-yl)-[6-phenyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine (II-20): Prepared in 32% yield. ^1H NMR (500 MHz, DMSO) δ 6.94 (1H, $J=7.4$ Hz, t), 7.24 (1H, $J=7.4$ Hz, t), 7.33 (1H, $J=8.4$ Hz, d), 7.42 (3H, m), 7.57 (1H, $J=7.3$ Hz, t), 7.68 (2H, m), 7.75 (1H, $J=7.9$ Hz, d), 7.93 (3H, m), 8.18 (1H, br s), 10.45 (1H, br s), 12.5 (1H, br s) ppm; HPLC-Method A, R_t 4.0 min; MS (FIA) 432.2 (M+H)⁺.

Example 21 (*1H-Indazol-3-yl*)-[6-(pyridin-4-yl)-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine (II-21):

Prepared in 12% yield. $^1\text{HNMR}$ (500 MHz, DMSO) δ 7.16 (1H, J=7.4 Hz, t), 7.46 (1H, J=7.6 Hz, t), 7.56 (1H, J=8.3 Hz, d), 7.80 (1H, J=7.2 Hz, t), 7.90 (2H, m), 7.97 (1H, J=7.8 Hz, d), 8.09 (1H, br), 8.22 (2H, J=4.9 Hz, d), 8.45 (1H, br s), 8.93 (2H, J=4.8 Hz, d), 10.9 (1H, br s), 12.8 (1H, br s) ppm; HPLC-Method A, R_t 3.307 min; MS (FIA) 433.2 (M+H)⁺

10

Example 22 (*1H-Indazol-3-yl*)-[6-(pyridin-2-yl)-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine (II-22):

Prepared in 42% yield. $^1\text{HNMR}$ (500 MHz, DMSO) δ 7.07 (1H, J=7.4 Hz, t), 7.36 (1H, J=7.4 Hz, t), 7.46 (1H, J=7.4 Hz, d), 7.53 (1H, J=5.0 Hz, t), 7.70 (1H, J=7.4 Hz, t), 7.79 (1H, J=7.1 Hz, t), 7.83 (1H, J=7.4 Hz, d), 7.88 (1H, J=7.8 Hz, d), 7.97 (1H, J=7.7 Hz, t), 8.02 (1H, J=5.5 Hz, br d), 8.36 (1H, J=7.8 Hz, d), 8.75 (2H, J=4.1 Hz, d), 10.5 (1H, br s), 12.7 (1H, br s) ppm; HPLC-Method A, R_t 3.677 min; MS (FIA) 433.2 (M+H)⁺.

Example 23 [6-(2-Chlorophenyl)-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]-(*1H-indazol-3-yl*)-amine (II-23):

Prepared in 44% yield; $^1\text{HNMR}$ (500 MHz, DMSO) δ 7.08 (1H, J=7.5 Hz, t), 7.37 (1H, J=7.5 Hz, t), 7.45 (1H, J=8.4 Hz, d), 7.51 (2H, m), 7.61 (1H, J=7.4, 1.9 Hz, dd), 7.69 (2H, m), 7.79 (2H, J=4.0 Hz, d), 7.86 (3H, J=7.8 Hz, d), 8.04 (2H, J=6.2 Hz, br d), 10.7 (1H, br s), 12.6 (1H, br s) ppm; HPLC-Method A, R_t 3.552 min; MS (FIA) 466.2 (M+H)⁺.

30

Example 24 [5,6-Dimethyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]-(*1H-indazol-3-yl*)-amine (II-24): Prepared in 35% yield; mp 183-186°C: $^1\text{HNMR}$ (500 MHz, DMSO) δ 2.14

(3H, s), 2.27 (3H, s), 6.85 (1H, J=7.5 Hz, t), 7.15 (1H, J=7.6 Hz, t), 7.32 (3H, m), 7.38 (1H, J=7.5 Hz, t), 7.42 (1H, J=7.4 Hz, t), 7.53 (1H, J=7.6 Hz, d), 8.88 (1H, s), 12.5 (1H, s) ppm; HPLC-Method A, R_t 2.889 min.; MS (FIA) 5 384.2 (M+H)⁺.

Example 25 [5,6-Dimethyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]-(5-fluoro-1H-indazol-3-yl)-amine (II-25): Prepared in 44% yield. Melting point 160-163°C; ¹HNMR 10 (500 MHz, DMSO) δ 2.27 (3H, s), 2.40 (3H, s), 7.16 (2H, m), 7.44 (2H, m), 7.52 (1H, J=7.4 Hz, t), 7.57 (1H, J=7.4 Hz, t), 7.67 (1H, J=7.8 Hz, d), 9.03 (1H, s), 12.75 (1H, s) ppm; HPLC-Method A, R_t 2.790 min; MS (FIA) 402.2 (M+H)⁺.

15 Example 26 [2-(2-Chlorophenyl)-5,6-dimethyl-pyrimidin-4-yl]-(1H-indazol-3-yl)-amine (II-26): Prepared in 30% yield. ¹HNMR (500 MHz, DMSO) δ 2.14 (3H, s), 2.33 (3H, s), 6.84 (1H, J=7.4 Hz, t), 7.13 (1H, J=7.4 Hz, t), 7.19 (1H, J=6.9 Hz, br t), 7.27 (1H, J=7.4 Hz, d), 7.32 (3H, br m), 7.37 (1H, J=7.1 Hz, d), 10.0 (1H, br), 12.8 (1H, br s) ppm; δ 2.919 min; MS (FIA) 350.1 (M+H)⁺.

25 Example 27 [5,6-Dimethyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]-(7-fluoro-1H-indazol-3-yl)-amine (II-27): Prepared in 92% yield. ¹HNMR (500 MHz, DMSO) δ 2.33 (3H, s), 2.50 (3H, s), 6.97 (1H, m), 7.15 (1H, m), 7.30 (1H, J=8.1 Hz, d), 7.65 (3H, m), 7.76 (1H, J=7.5 Hz, d), 10.0 (1H, s), 13.4 (1H, s) ppm; HPLC-Method A, R_t 3.053 30 min; MS (FIA) 402.2 (M+H)⁺.

Example 28 (5,7-Difluoro-1H-indazol-3-yl)-[5,6-Dimethyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine (II-

28). Prepared in 50% yield. $^1\text{H}\text{NMR}$ (500 MHz, DMSO) δ 2.42 (3H, s), 2.63 (3H, s), 7.22 (1H, $J=7.6$ Hz, d), 7.38 (1H, $J=9.3$, 1.7 Hz, dt), 7.71 (1H, m), 7.75 (1H, $J=7.0$ Hz, d), 7.79 (1H, $J=6.7$ Hz, d), 7.86 (1H, $J=8.0$ Hz, d), 10.0 (1H, s), 13.2 (1H, s) ppm; HPLC-Method A, R_t 3.111 min; MS (FIA) 420.2 ($M+H$) $^+$.

Example 29 [2-(2-Chlorophenyl)-5,6-dimethyl-pyrimidin-4-yl]-(5,7-difluoro-1H-indazol-3-yl)-amine (II-29):

10 Prepared in 58% yield. $^1\text{H}\text{NMR}$ (500 MHz, DMSO) δ 2.47 (3H, s), 2.66 (3H, s), 7.44 (2H, m), 7.53 (1H, m), 7.64 (3H, m), 10.4 (1H, br), 13.8 (1H, br s) ppm; HPLC-Method A, R_t 2.921 min; MS (FIA) 386.1 ($M+H$) $^+$.

15 Example 30 [2-(2-Chlorophenyl)-5,6-dimethyl-pyrimidin-4-yl]-(7-fluoro-1H-indazol-3-yl)-amine (II-30): Prepared in 70% yield. $^1\text{H}\text{NMR}$ (500 MHz, DMSO) δ 2.35 (3H, s), 2.51 (3H, s), 7.03 (1H, $J=7.8$, 4.4 Hz, dt), 7.22 (1H, m), 7.33 (1H, $J=7.4$ Hz, t), 7.42 (1H, m), 9.19 (1H, s), 13.3 (1H, s) ppm; HPLC-Method A, R_t 2.859 min; MS (FIA) 368.2 ($M+H$) $^+$.

25 Example 31 [2-(2-Chlorophenyl)-5,6-dimethyl-pyrimidin-4-yl]-(5-fluoro-1H-indazol-3-yl)-amine (II-31): Prepared in 86% yield. $^1\text{H}\text{NMR}$ (500 MHz, DMSO) δ 2.49 (3H, s), 2.68 (3H, s), 7.38 (1H, $J=9.0$ Hz, t), 7.54 (2H, m), 7.67 (4H, m), 10.5 (1H, br), 13.2 (1H, br s) ppm; HPLC-Method A, R_t 2.850 min; MS (FIA) 368.1 ($M+H$) $^+$.

30 Example 32 [2-(2,4-Dichlorophenyl)-5,6-dimethyl-pyrimidin-4-yl]-(1H-indazol-3-yl)-amine (II-32): Prepared in 52% yield. $^1\text{H}\text{NMR}$ (500 MHz, DMSO) δ 2.46 (3H, s), 2.64

(3H, s), 7.16 (1H, J=7.5 Hz, t), 7.46 (1H, J=7.6 Hz, t), 7.61 (2H, m), 7.68 (2H, J=8.2 Hz, d), 7.82 (1H, m), 10.2 (1H, br), 13.0 (1H, br s) ppm; HPLC-Method A, R_t 2.983 min; MS (FIA) 384.1 (M+H).

5

Example 33 (5-Methyl-2*H*-pyrazol-3-yl)-[2-(2-methylphenyl)-quinazolin-4-yl]-amine (II-33): ¹HNMR (DMSO) δ 1.21 (3H, s), 2.25 (3H, s), 6.53 (1H, s), 7.38 (4H, m), 7.62 (1H, d), 7.73 (1H, d), 7.81 (1H, d), 7.89 (1H, t), 8.70 (1H, s), 12.20 (1H, s); MS 316.3 (M+H)⁺.

Example 34 [2-(2,4-Difluorophenyl)-quinazolin-4-yl]-(5-methyl-2*H*-pyrazol-3-yl)-amine (II-34): ¹HNMR (500 MHz, DMSO-d6) δ 12.4 (br s, 1H), 10.8 (br s, 1H), 8.58 (d, 1H), 7.97 (m, 1H), 8.36 (m, 1H), 7.85 (m, 1H), 7.60 (m, 1H), 6.62 (s, 1H), 2.30 (s, 3H); MS 338.07 (M+H).

Example 35 [2-(2,5-Dimethoxyphenyl)-quinazolin-4-yl]-(5-methyl-2*H*-pyrazol-3-yl)-amine (II-35): ¹HNMR (500 MHz, DMSO-d6) δ 12.5 (br s, 1H), 8.68 (br, 1H), 7.92 (t, J = 7.5 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.45 (s, 1H), 7.14 (m, 2H), 6.51 (s, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 2.14 (s, 3H); MS 362.2 (M+H).

Example 36 [2-(2-Chlorophenyl)-quinazolin-4-yl]-(5-methyl-2*H*-pyrazol-3-yl)-amine (II-36): ¹HNMR (500 MHz, DMSO-d6) δ 11.8 (br, 1H), 8.80 (d, J = 8.3 Hz, 1H), 8.00 (t, J = 7.6 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.78 (m, 2H), 7.67 (d, J = 7.8 Hz, 1H), 7.61 (t, J = 7.0 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 6.56 (s, 1H), 2.18 (s, 3H); MS 336.1 (M+H).

Example 37 [2-(2-Methoxyphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (II-37): ^1H NMR (500 MHz, DMSO-d₆) δ 8.78 (s, br, 1H), 8.00 (t, J = 7.4 Hz, 1H), 7.90 (m, 2H), 7.74 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.3 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 6.58 (s, br, 1H), 3.90 (s, 3H), 2.21 (s, 3H); MS 332.1 (M+H).

Example 38 [2-(2,6-Dimethylphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (II-38): ^1H NMR (500 MHz, DMSO-d₆) δ 12.2 (s, br, 2H), 8.88 (d, J = 7.7 Hz, 1H), 8.05 (t, J = 7.7 Hz, 1H), 7.80 (m, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 7.7 Hz, 2H), 6.36 (s, 1H), 2.16 (s, 3H), 2.15 (s, 6H); MS 330.1 (M+H).

Example 39 [2-(2-Acetylphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (II-39): ^1H NMR (500 MHz, DMSO-d₆) δ 12.35 (s, br, 1H), 8.93 (d, J = 8.4 Hz, 1H), 8.37 (d, J = 8.6 Hz, 1H), 8.20 (d, J = 7.6 Hz, 1H), 8.11 (t, J = 8.0 Hz, 2H), 7.89 (m, 2H), 7.77 (m, 2H), 6.93 (s, 1H), 2.33 (s, 3H), 2.04 (s, 3H). MS 344.1 (M+H).

Example 40 [2-(2,3-Dimethylphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (II-40): ^1H NMR (500 MHz, DMSO-d₆) δ 12.6 (s, br, 1H), 12.1 (s, br, 1H), 8.91 (d, J = 7.7 Hz, 1H), 8.14 (t, J = 7.2 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 7.0 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 6.60 (s, 1H), 2.43 (s, 3H), 2.35 (s, 3H), 2.32 (s, 3H); MS 330.1 (M+H).

Example 41 (5-Methyl-2H-pyrazol-3-yl)-[2-(2-trifluoromethylphenyl)-quinazolin-4-yl]-amine (II-41):

¹HNMR (500 MHz, DMSO-d₆) δ 12.3 (s, 1H), 10.5 (s, 1H), 8.77 (d, J = 8.2 Hz, 1H), 7.92 (m, 2H), 7.85 (m, 3H), 7.56 (t, J = 8.1 Hz, 1H), 7.67 (t, J = 7.4 Hz, 1H), 6.63 (s, 1H), 2.27 (s, 3H); MS 370.1 (M+H).

5

Example 42 [2-(2-Ethylphenyl)-quinazolin-4-yl]-(5-Methyl-2H-pyrazol-3-yl)-amine (II-42): ¹HNMR (500 MHz, DMSO-d₆) δ 8.80 (m, 1H), 8.02 (s, br, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.77 (m, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.54 (m, 1H), 7.41 (m, 2H), 6.40 (s, 1H), 2.75 (q, J = 7.1 Hz, 2H), 2.17 (s, 3H), 0.99 (t, J = 7.5 Hz, 3H); MS 330.1 (M+H).

Example 43 (2-Biphenyl-2-yl-quinazolin-4-yl)-(5-methyl-2H-pyrazol-3-yl)-amine (II-43): ¹HNMR (500 MHz, DMSO-d₆) δ 8.76 (d, J = 7.6 Hz, 1H), 8.04 (m, 1H), 7.75 (m, 6H), 7.30 (m, 5H), 5.34 (s, 1H), 2.14 (s, 3H); MS 378.2 (M+H).

Example 44 [2-(2-Hydroxyphenyl)-quinazolin-4-yl]-(5-Methyl-2H-pyrazol-3-yl)-amine (II-44): ¹HNMR (500 MHz, DMSO-d₆) δ 10.9 (s, br, 1H), 8.62 (d, J = 8.2 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.87 (m, 2H), 7.60 (t, J = 7.9 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 6.92 (m, 2H), 6.45 (s, 1H), 2.27 (s, 3H); MS 318.1 (M+H).

25

Example 45 [2-(2-Ethoxyphenyl)-quinazolin-4-yl]-(5-Methyl-2H-pyrazol-3-yl)-amine (II-45): ¹HNMR (500 MHz, DMSO-d₆) δ 12.1 (s, br, 1H), 8.75 (d, J = 8.3 Hz, 1H), 7.97 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.55 (s, 1H), 4.11 (q, J = 6.9 Hz, 2H), 2.16 (s, 3H), 1.22 (t, J = 6.9 Hz, 3H); MS 346.1 (M+H).

Example 46 [5-(Thiophen-2-yl)-2H-pyrazol-3-yl]-[2-(2-trifluoromethylphenyl)-quinazolin-4-yl]-amine (II-46) :

5 ^1H NMR (500 MHz, DMSO-d₆) δ 8.04 (d, J = 8.3 Hz, 1H), 8.05
 (dd, J = 7.3, 8.2 Hz, 1H), 7.93 (d, J = 6.5 Hz, 1H), 7.81
 (m, 5H), 7.34 (d, J = 5.0 Hz, 1H), 7.25 (m, 1H), 7.00 (m,
 1H), 6.87 (s, 1H); MS 438.1 (M+H).

10 Example 47 [4-(Thiophen-2-yl)-2H-pyrazol-3-yl]-[2-(2-trifluoromethylphenyl)-quinazolin-4-yl]-amine (II-47) :

Prepared according to Method B. ^1H NMR (500MHz, DMSO-d₆) δ
6.97 (m, 1H), 7.08 (m, 1H), 7.27 (m, 1H), 7.36 (m, 1H),
7.66 (m, 2H), 7.77 (m, 3H), 7.83 (m, 1H), 8.00 (m, 1H),
8.18 (s, 1H), 8.62 (d, J = 8.2 Hz, 1H), 10.7 (br. s, 1H);
15 EI-MS 438.1 (M+H); HPLC-Method A, R_t 2.97 min.

Example 48 (4-Phenyl-2H-pyrazol-3-yl)-[2-(2-trifluoromethylphenyl)-quinazolin-4-yl]-amine (II-48) :

Prepared according to Method B. ^1H NMR (500MHz, DMSO-d₆) δ
20 7.05 (br. s, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.25 (m, 3H),
7.43 (m, 2H), 7.60 (m, 2H), 7.73 (m, 2H), 7.80 (d, 1H),
7.95 (m, 1H), 8.12 (br. s, 1H), 8.60 (m, 1H), 10.6 (br.
s, 1H); EI-MS 432.2 (M+H); HPLC-Method A, R_t 3.04 min.

25 Example 49 (5-tert-Butyl-2H-pyrazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-49) :

^1H NMR (500 MHz, DMSO-d₆) δ 8.76 (d, J = 8.3 Hz, 1H), 7.94
(m, 2H), 7.79 (m, 4H), 7.70 (t, J = 7.6 Hz, 1H), 6.51 (s,
1H), 1.16 (s, 9H); MS 412.2 (M+H).

30 Example 50 (5-Phenyl-2H-pyrazol-3-yl)-[2-(2-trifluoromethylphenyl)-quinazolin-4-yl]-amine (II-50) :

^1H NMR (500MHz, DMSO-d₆) δ 7.09 (s, 1H), 7.36 (td, J = 7.8,

1.1 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.65 (br. d, J =
8.1 Hz, 2H), 7.78 (m, 2H), 7.90 (m, 4H), 7.95 (d, J = 7.7
Hz, 1H), 8.00 (t, J = 7.8 Hz, 1H), 8.81 (d, J = 8.6 Hz,
1H), 11.29 (br. s, 1H); EI-MS 432.1 (M+H); HPLC-Method A,
5 R_t 3.24 min.

Example 51 (4,5-Diphenyl-2H-pyrazol-3-yl)-[2-(2-trifluoromethylphenyl)-quinazolin-4-yl]-amine (II-51):
¹HNMR (500MHz, DMSO-d6) δ 7.13 (m, 1H), 7.18 (m, 5H), 7.36
10 (m, 5H), 7.62 (m, 3H), 7.73 (m, 2H), 7.85 (m, 1H), 8.48
(d, J = 8.7 Hz, 1H), 10.02 (s, 1H), 13.19 (s, 1H); EI-MS
508.2 (M+H); HPLC-Method A, R_t 3.39 min.

Example 52 (4-Carbamoyl-2H-pyrazol-3-yl)-[2-(2-trifluoromethylphenyl)-quinazolin-4-yl]-amine (II-52):
Prepared in 40% yield. ¹HNMR (500MHz, DMSO-d6): δ 12.85
(s, 1H), 12.77 (s, 1H), 11.80 (s, 1H), 10.80 (s, 1H),
8.35-7.42 (m, 9H); MS 399.13 (M+H) HPLC-Method A, R_t
2.782 min.

20
Example 53 (2H-Pyrazol-3-yl)-[2-(2-trifluoromethylphenyl)-quinazolin-4-yl]-amine (II-53):
Prepared in 38% yield. ¹HNMR (500 MHz, DMSO-d6) δ 12.52
(s, 1H), 10.65 (s, 1H), 8.75 (d, 1H), 7.91-7.68 (m, 8H),
25 6.87 (s, 1H). MS: (M+H) 356.17. HPLC-Method A, R_t 2.798
min.

Example 54 (5-Hydroxy-2H-pyrazol-3-yl)-[2-(2-trifluoromethylphenyl)-quinazolin-4-yl]-amine (II-54):
30 Prepared in 36% yield; ¹HNMR (500 MHz, DMSO-d6) δ 10.61
(s, 1H), 8.75 (s, 1H), 8.03-7.75 (m, 9H), 5.97 (s, 1H);
MS 372.18 (M+H); HPLC-Method A, R_t 2.766 min.

Example 55 (5-Cyclopropyl-2H-pyrazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-55): Prepared in 30% yield. $^1\text{HNMR}$ (500 MHz, DMSO-d₆) δ 12.21 (s, 1H), 10.45 (s, 1H), 8.68 (s, 1H), 7.89-7.45 (m, 8H), 6.48 (s, 1H), 0.89 (m, 2H), 0.62 (s, 2H). MS 396.18 (M+H); HPLC-Method A, R_t 3.069 min.

Example 56 (5-Methoxymethyl-2H-pyrazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-56): 10 Prepared in 33% yield; $^1\text{HNMR}$ (500 MHz, DMSO-d₆) δ 12.51 (s, 1H), 10.48 (s, 1H), 8.60 (s, 1H), 7.81-7.55 (m, 7H), 6.71 (s, 1H), 4.28 (s, 2H), 3.18 (s, 3H). MS 400.19 (M+H); HPLC-Method A, R_t 2.881 min.

15 Example 57 (1H-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-57): Prepared to afford 51 mg (78% yield) as pale yellow solid. $^1\text{HNMR}$ (500 MHz, DMSO-d₆) δ 12.7 (s, 1H), 10.4 (s, 1H), 8.55 (d, 1H), 7.81 (t, 1H), 7.71 (d, 1H), 7.61 (d, 1H), 7.58 (t, 1H), 7.46 (m, 4H), 7.36 (d, 1H), 7.22 (t, 1H), 6.91 (t, 1H) ppm; LC-MS (ES+) 406.16 (M+H), (ES-) 404.19 (M-H); HPLC-Method A, R_t 3.00 min.

Example 58 (4-Chloro-1H-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-58): 25 Prepared in DMF (70% yield) as pale yellow solid. $^1\text{HNMR}$ (500 MHz, DMSO-d₆) δ 13.3 (s, br, 1H), 10.9 (s, br, 1H), 8.60 (d, 1H), 7.97 (t, 1H), 7.81 (d, 1H), 7.75 (t, 1H), 7.67 (d, 1H), 7.63 (dd, 1H), 7.57 (m, 2H), 7.43 (d, 1H), 7.28 (dd, 1H), 7.08 (d, 1H) ppm; LC-MS (ES+) 440.10 (M+H), (ES-) 438.12 (M-H); HPLC-Method A, R_t 3.08 min.

Example 59 (5-Fluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-59): Prepared in DMF (34% yield) as pale yellow solid. ^1H NMR (500 MHz, DMSO-d₆) δ 13.0 (s, 1H), 10.6 (s, 1H), 8.72 (d, 1H), 7.99 (t, 1H), 7.89 (d, 1H), 7.79 (d, 1H), 7.75 (t, 1H), 7.68 (m, 3H), 7.56 (dd, 1H), 7.39 (d, 1H), 7.28 (t, 1H) ppm; LC-MS (ES+) 424.12 (M+H), (ES-) m/e= 422.13 (M-H); HPLC-Method A, R_t 3.05 min.

10 Example 60 (7-Fluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-60): Prepared in DMF (51% yield) as yellow solid. ^1H NMR (500 MHz, DMSO-d₆) δ 13.4 (s, 1H), 10.6 (s, 1H), 8.68 (d, 1H), 7.95 (t, 1H), 7.85 (d, 1H), 7.72 (m, 2H), 7.63 (m, 2H), 15 7.58 (m, 1H), 7.43 (d, 1H), 7.18 (dd, 1H), 7.00 (m, 1H) ppm; LC-MS (ES+) 424.11 (M+H), (ES-) 422.15 (M-H); HPLC-Method A, R_t 3.06 min.

20 Example 61 (5-Methyl-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-61): Prepared in DMF (81% yield) as yellow solid. ^1H NMR (500 MHz, DMSO-d₆) δ 13.0 (s, br, 1H), 8.79 (br, 1H), 8.11 (br, 1H), 7.96 (d, 1H), 7.82 (m, 5H), 7.46 (s, 1H), 7.41 (d, 1H), 7.20 (d, 1H), 2.33 (s, 3H) ppm; MS (ES+) 420.15 (M+H), (ES-) 418.17 (M-H); HPLC-Method A, R_t 3.07 min.

25 Example 62 [2-(2,6-Dichloro-phenyl)-quinazolin-4-yl]-[5-fluoro-1*H*-indazol-3-yl]-amine (II-62): Prepared in DMF (37% yield) as yellow solid. ^1H NMR (500 MHz, DMSO-d₆) 30 δ 13.0 (s, 1H), 10.8 (s, 1H), 8.72 (d, 1H), 7.97 (t, 1H), 7.90 (d, 1H), 7.75 (t, 1H), 7.53 (m, 3H), 7.43 (t, 1H), 7.35 (d, 1H), 7.23 (t, 1H) ppm; LCMS (ES+) 424.08 (M+H), (ES-) 422.10 (M-H); HPLC-Method A, R_t 3.06 min.

Example 63 [2-(2-Chloro-phenyl)-quinazolin-4-yl]-[1H-indazol-3-yl]-amine (II-63): Prepared in 91% yield. $^1\text{H}\text{NMR}$ (500MHz, DMSO-d6) δ 7.06 (t, 1H), 7.36 (t, 1H), 7.39 (t, 1H), 7.52 (m, 3H), 7.62 (d, 1H), 7.72 (d, 1H), 7.82 (m, 1H), 7.90 (d, 1H), 8.05 (m, 1H), 8.76 (d, 1H), 11.5 (m, 1H), 13.02 (s, 1H); EI-MS 372.1 (M+1); HPLC-Method A, R_t 2.93 min.

10 Example 64 (5-Trifluoromethyl-1H-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-64): Prepared in DMF (57% yield) as yellow solid. $^1\text{H}\text{NMR}$ (500 MHz, DMSO-d6) δ 13.4 (s, br, 1H), 11.4 (br, 1H), 8.72 (d, 1H), 8.12 (s, 1H), 7.98 (t, 1H), 7.83 (d, 1H), 7.76 (d, 1H), 7.73 (dd, 1H), 7.60 (m, 4H), 7.52 (d, 1H) ppm; LC-MS (ES+) 474.12 (M+H), (ES-) 472.17 (M-H); HPLC-Method A, R_t 3.25 min.

20 Example 65 (4-Trifluoromethyl-1H-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-65): Prepared in DMF (8% yield) as yellow solid. $^1\text{H}\text{NMR}$ (500 MHz, DMSO-d6) δ 13.7 (s, br, 1H), 11.2 (br, 1H), 8.70 (d, 1H), 8.05 (s, 1H), 7.85 (m, 3H), 7.65 (m, 4H), 7.51 (m, 2H) ppm; LC-MS (ES+) 474.13 (M+H), (ES-) 472.17 (M-H); HPLC-Method A, R_t 3.15 min.

25 Example 66 [2-(2,6-Dichloro-phenyl)-quinazolin-4-yl]-[1H-indazol-3-yl]-amine (II-66): Prepared in DMF (30% yield) as yellow solid. $^1\text{H}\text{NMR}$ (500 MHz, DMSO-d6) δ 12.9 (s, 1H), 11.1 (s, 1H), 8.69 (d, 1H), 7.95 (t, 1H), 7.82 (d, 1H), 7.73 (t, 1H), 7.56 (d, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.39 (m, 2H), 7.26 (t, 1H), 6.92 (t, 1H) ppm; LC-MS (ES+)

406.11 (M+H), (ES-) 404.12 (M-H); HPLC-Method A, R_t 3.00 min.

Example 67 (*1H-indazol-3-yl*)-[2-(2-methyl-phenyl)-5 quinazolin-4-yl]-amine (II-67): Prepared in 55% yield.

¹HNMR (500MHz, DMSO-d6) δ 2.15 (s, 3H), 7.09 (t, 1H), 7.26 (d, 1H), 7.31 (t, 1H), 7.39 (t, 1H), 7.42 (m, 1H), 7.55 (d 1H), 7.64 (d, 1H), 7.74 (d, 1H), 7.89 (m, 1H), 7.96 (d, 1H), 8.10 (m, 1H), 8.81 (d, 1H), 12.0 (m, 1H), 13.18 (s, 1H); EI-MS 352.2 (M+1); HPLC-Method A, R_t 2.93 min.

Example 68 (7-Trifluoromethyl-*1H-indazol-3-yl*)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-68): Prepared in DMF (75% yield) as yellow solid. ¹HNMR (500 MHz, DMSO-d6) δ 13.5 (s, br, 1H), 11.2 (s, br, 1H), 8.68 (d, 1H), 7.97 (t, 1H), 7.92 (d, 1H), 7.82 (d, 1H), 7.74 (t, 1H), 7.70 (d, 1H), 7.68 (d, 1H), 7.64 (m, 2H), 7.57 (m, 1H), 7.14 (t, 1H) ppm; LC-MS (ES+) 474.11 (M+H), (ES-) 472.14 (M-H); HPLC-Method A, R_t 3.24 min.

Example 69 (6-Trifluoromethyl-*1H-indazol-3-yl*)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-69): Prepared by Method B in DMF (78% yield) as yellow solid. ¹HNMR (500 MHz, DMSO-d6) δ 13.4 (s, br, 1H), 11.1 (s, br, 1H), 8.67 (d, 1H), 7.95 (t, 1H), 7.82 (m, 3H), 7.72 (m, 2H), 7.63 (m, 2H), 7.57 (t, 1H), 7.23 (d, 1H) ppm; LC-MS (ES+) 474.12 (M+H), (ES-) 472.15 (M-H); HPLC-Method A, R_t 3.28 min.

Example 70 (5-Nitro-*1H-indazol-3-yl*)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-70): Prepared in DMF (82% yield) as yellow solid. ¹HNMR (500 MHz, DMSO-d6) δ 13.6 (s, br, 1H), 11.4 (s, br, 1H), 8.75

(s, 1H), 8.72 (d, 1H), 8.09 (dd, 1H), 7.98 (t, 1H), 7.83 (d, 1H), 7.75 (t, 1H), 7.70 (m, 2H), 7.61 (m, 3H) ppm; LC-MS (ES+) 451.14 (M+H), (ES-) 449.12 (M-H); HPLC-Method A, R_t 3.02 min.

5

Example 71 (5,7-Difluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-71): Prepared in DMF (60% yield) as yellow solid. ¹HNMR (500 MHz, DMSO-d6) δ 13.7 (s, br, 1H), 11.2 (s, br, 1H), 8.73 (d, 1H), 8.03 (t, 1H), 7.88 (d, 1H), 7.80 (m, 2H), 7.70 (m, 3H), 7.32 (m, 2H) ppm; LC-MS (ES+) 442.14 (M+H), (ES-) 440.14 (M-H); HPLC-Method A, R_t 3.11 min.

Example 72 (4-Pyrrol-1-yl-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-72): Prepared in DMF (33% yield) as yellow solid. ¹HNMR (500 MHz, DMSO-d6) δ 13.4 (s, br, 1H), 11.0 (s, br, 1H), 8.53 (d, 1H), 7.98 (t, 1H), 7.75 (m, 4H), 7.62 (m, 2H), 7.52 (d, 1H), 7.43 (t, 1H), 7.05 (d, 1H), 6.80 (s, 2H), 5.61 (s, 2H) ppm; LC-MS (ES+) 471.18 (M+H), (ES-) 469.18 (M-H); HPLC-Method A, R_t 3.12 min.

Example 73 (5-Amino-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-73): A solution of compound II-70 (70 mg, 0.16 mmol) in MeOH (2 mL) was treated with Raney Ni until solution was colorless (about 1.5 g Raney Ni was added). After stirring at room temperature for 40 min, the mixture was filtered through celite, the resulting celite was washed with MeOH (5 times), and the solvent was evaporated *in vacuo* to provide a crude product that was then purified by HPLC to give the title compound as a yellow solid (10 mg, 15%). m.p. 221-223°C; ¹HNMR (500 MHz, DMSO-d6)

δ 13.2 (s, br, 1H), 10.7 (s, br, 1H), 9.80 (br, 2H), 8.68 (d, 1H), 7.97 (t, 1H), 7.87 (d, 1H), 7.75 (m, 2H), 7.65 (m, 5H), 7.30 (d, 1H) ppm; MS (ES+) 421.16 (M+H), (ES-) 419.17 (M-H); HPLC-Method A, R_t 2.41 min.

5

Example 74 [2-(2-Chloro-phenyl)-quinazolin-4-yl]- (7-fluoro-1H-indazol-3-yl)-amine (II-74): Prepared in DMF (35% yield) as yellow solid. ¹HNMR (500 MHz, DMSO-d6) δ 13.7 (s, 1H), 11.7 (s, br, 1H), 8.80 (d, 1H), 8.15 (t, 1H), 7.99 (d, 1H), 7.88 (t, 1H), 7.68 (d, 1H), 7.60 (m, 2H), 7.53 (t, 1H), 7.46 (t, 1H), 7.25 (dd, 1H), 7.04 (m, 1H) ppm; LC-MS (ES+) 390.16 (M+H); HPLC-Method A, R_t 3.00 min.

15 Example 75 [2-(2-Chloro-phenyl)-quinazolin-4-yl]- (5-fluoro-1H-indazol-3-yl)-amine (II-75): Prepared in DMF. ¹HNMR (500 MHz, DMSO-d6) δ 13.2 (s, 1H), 11.7 (s, br, 1H), 8.80 (d, 1H), 8.10 (t, 1H), 7.91 (m, 2H), 7.70 (d, 1H), 7.58 (m, 4H), 7.50 (t, 1H), 7.29 (t, 1H) ppm; LC-MS (ES+) 390.17 (M+H); HPLC-Method A, R_t 3.00 min.

20 Example 76 [2-(2-Chloro-phenyl)-quinazolin-4-yl]- (5,7-difluoro-1H-indazol-3-yl)-amine (II-76): Prepared in DMF (55% yield) as yellow solid. ¹HNMR (500 MHz, DMSO-d6) δ 13.8 (s, 1H), 11.5 (s, br, 1H), 8.76 (d, 1H), 8.08 (t, 1H), 7.93 (d, 1H), 7.84 (t, 1H), 7.64 (d, 1H), 7.55 (d, 1H), 7.50 (t, 1H), 7.44 (m, 2H), 7.36 (t, 1H) ppm; LC-MS (ES+) 408.15 (M+H), (ES-) 406.17 (M-H); HPLC-Method A, R_t 3.08 min.

30

Example 77 [2-(2-Chloro-phenyl)-quinazolin-4-yl]- (5-trifluoromethyl-1H-indazol-3-yl)-amine (II-77): Prepared in DMF (66% yield) as yellow solid. ¹HNMR (500 MHz, DMSO-

d6) δ 13.5 (s, 1H), 11.4 (s, br, 1H), 8.79 (d, 1H), 8.29 (s, 1H), 8.07 (t, 1H), 7.93 (d, 1H), 7.84 (t, 1H), 7.72 (d, 1H), 7.63 (d, 2H), 7.53 (d, 1H), 7.48 (t, 1H), 7.36 (t, 1H) ppm; LC-MS (ES+): m/e= 440.16 (M+H); (ES-): m/e= 5 438.18 (M-H); HPLC-Method A, R_t 3.22 min.

Example 78 [2-(2-cyano-phenyl)-quinazolin-4-yl]-[1*H*-indazol-3-yl]-amine (II-78): Prepared in 13% yield. ¹H-NMR (500 MHz, DMSO) δ 12.9 (br, 1H), 10.8 (br, 1H), 8.73 (br s, 1H), 7.97 (m, 4H), 7.74 (m, 1H), 7.5 (m, 4H), 7.42 (m, 1H), 7.08 (m, 1H) ppm; MS (FIA) 363.2 (M+H); HPLC-Method A, R_t 2.971 min.

Example 79 (5-Bromo-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-79): Prepared in DMF (64% yield) as yellow solid. ¹H-NMR (500 MHz, DMSO-d6) δ 13.4 (s, 1H), 11.6 (s, br, 1H), 8.93 (d, 1H), 8.21 (t, 1H), 8.14 (s, 1H), 8.05 (d, 1H), 7.95 (m, 4H), 7.86 (t, 1H), 7.65 (d, 1H), 7.59 (d, 1H) ppm; MS (ES+) 486.10 (M+H), (ES-) 484.09 (M-H); HPLC-Method A, R_t 20 3.22 min.

Example 80 (6-Chloro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-80): Prepared in DMF (94% yield) as yellow solid. ¹H-NMR (500 MHz, DMSO-d6) δ 13.1 (s, 1H), 11.2 (s, br, 1H), 8.73 (d, 1H), 8.03 (t, 1H), 7.87 (d, 1H), 7.79 (m, 2H), 7.73 (m, 2H), 7.67 (m, 2H), 7.58 (s, 1H), 7.04 (dd, 1H) ppm. LC-MS (ES+) 440.14 (M+H), (ES-) 438.16 (M-H); HPLC-Method A, R_t 30 3.25 min.

Example 81 (7-Fluoro-6-trifluoromethyl-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-

81): Prepared in DMF (30% yield) as yellow solid. ^1H NMR (500 MHz, DMSO-d6) δ 13.9 (s, 1H), 11.0 (s, br, 1H), 8.64 (d, 1H), 7.94 (t, 1H), 7.81 (d, 1H), 7.71 (m, 2H), 7.60 (m, 4H), 7.20 (dd, 1H) ppm. LC-MS (ES+) 492.18 (M+H), 5 (ES-) 490.18 (M-H); HPLC-Method A, R_t 3.44 min.

Example 82 (6-Bromo-1H-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-82): Prepared in DMF (40% yield) as yellow solid. ^1H NMR (500 MHz, DMSO-d6) δ 13.1 (s, 1H), 11.2 (s, br, 1H), 8.73 (d, 1H), 8.03 (t, 1H), 7.87 (d, 1H), 7.80 (m, 2H), 7.73 (m, 3H), 7.67 (m, 1H), 7.61 (d, 1H), 7.15 (dd, 1H) ppm; MS (ES+) 486.07 (M+H); HPLC-Method A, R_t 3.28 min.

Example 83 [2-(2,4-Bis-trifluoromethyl-phenyl)-quinazolin-4-yl]- (5,7-difluoro-1H-indazol-3-yl)-amine (II-83): Prepared in DMF in 28% yield. ^1H NMR (500MHz, MeOH-d4) δ 8.81 (d, $J=8.4\text{Hz}$, 1H), 8.35-8.20 (m, 3H), 8.19-7.96 (m, 3H), 7.40-7.34 (m, 1H), 7.29-7.14 (m, 1H); LC-MS (ES+) 510.14 (M+H); HPLC-Method C, R_t 8.29 min.

Example 84 (5,7-Difluoro-1H-indazol-3-yl)-[2-(4-fluoro-2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-84): Prepared in 48% yield. ^1H NMR (500MHz, MeOH-d4) δ 8.74-8.63 (m, 1H), 8.23-8.10 (m, 1H), 7.99-7.90 (m, 2H), 7.89-7.80 (m, 1H), 7.71-7.61 (m, 1H), 7.61-7.50 (m, 1H), 7.24-7.15 (m, 1H), 7.14-7.02 (m, 1H); LC-MS (ES+) 460.14 (M+H); HPLC-Method C, R_t 7.59 min.

Example 85 [2-(2-Bromo-phenyl)-quinazolin-4-yl]- (5,7-difluoro-1H-indazol-3-yl)-amine (II-85): Prepared in THF (21% yield). ^1H NMR (500MHz, MeOH-d4) δ 8.81 (d, $J=8.4\text{Hz}$, 1H), 8.35-8.20 (m, 3H), 8.19-7.96 (m, 3H), 7.40-7.34 (m,

1H), 7.29-7.14 (m, 1H); LC-MS (ES+) 510.14 (M+H); HPLC-
Method C, R_t 8.29 min.

Example 86 (5,7-Difluoro-1*H*-indazol-3-yl)-[2-(5-fluoro-2-
5 trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-86):

Prepared in THF (26% yield). ¹HNMR (500MHz, MeOH-d4) δ 8.62 (d, J=8.4Hz, 1H), 8.16-8.02 (m, 1H), 7.96-7.73 (m, 3H), 7.59-7.48 (m, 1H), 7.48-7.35 (m, 1H), 7.21-7.09 (m, 1H), 7.09-6.89 (m, 1H); LC-MS (ES+) 460.16 (M+H); HPLC-
10 Method C, R_t 7.28 min.

Example 87 [2-(2,4-Dichloro-phenyl)-quinazolin-4-yl]-
(5,7-Difluoro-1*H*-indazol-3-yl)-amine (II-87): Prepared in
THF (16% yield). ¹HNMR (500MHz, MeOH-d4) δ 8.81 (d,
15 J=8.4Hz, 1H), 8.35-8.20 (m, 3H), 8.19-7.96 (m, 3H), 7.40-
7.34 (m, 1H), 7.29-7.14 (m, 1H); LC-MS (ES+) 510.14
(M+H); HPLC-Method C, R_t 8.29 min.

Example 88 [2-(2-Chloro-5-trifluoromethyl-phenyl)-
20 quinazolin-4-yl]- (5,7-Difluoro-1*H*-indazol-3-yl)-amine
(II-88): Prepared in THF (33% yield). ¹HNMR (500MHz,
DMSO-d6) δ 10.76 (s, 1H), 8.66 (d, J=8.3Hz, 1H), 8.06-
7.84 (m, 3H), 7.81-7.63 (m, 3H); 7.48-7.16 (m, 2H); LC-MS
(ES+) 476.16 (M+H); HPLC-Method C, R_t 19.28 min.

25
Example 89 (4-Fluoro-1*H*-indazol-3-yl)-[2-(2-
trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-89):
Prepared in NMP (79% yield) as yellow solid. ¹HNMR (500
MHz, DMSO-d6) δ 13.2 (s, 1H), 10.8 (s, br, 1H), 8.63 (d,
30 1H), 7.97 (t, 1H), 7.85 (d, 1H), 7.74 (m, 2H), 7.64 (t,
1H), 7.57 (m, 2H), 7.32 (m, 2H), 6.82 (m, 1H) ppm; LC-MS
(ES+) 424.17 (M+H); HPLC-Method A, R_t 3.14 min.

Example 90 (*1H-Indazol-3-yl)-[8-methoxy-2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-90)*): Prepared using THF as solvent to afford the title compound as a TFA salt (23% yield). HPLC-Method A, R_t 2.97 min (95%); $^1\text{HNMR}$ (DMSO-d₆, 500 MHz) δ 12.9 (1H, bs), 11.0 - 10.7 (1H, bs), 8.25 (1H, m), 7.75-7.50 (8H, s), 7.30 (1H, m), 6.90 (1H, m), 4.0 (3H, s); MS (m/z) 436.2 (M+H).

Example 91 (*5-Fluoro-1H-indazol-3-yl)-[8-methoxy-2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-91)*): Prepared using TFA as solvent to afford the title compound as a TFA salt (23% yield). HPLC-Method A, R_t 3.10 min. (99%); $^1\text{HNMR}$ (DMSO-d₆, 500 MHz): 13.0 (1H, bs), 11.0 - 10.7 (1H, bs), 8.25 (1H, m), 7.75-7.50 (7H, m), 7.35 (1H, m), 7.25 (1H, m), 4.0 (3H, s); MS (m/z) 454.2 (M+H).

Example 92 (*7-Fluoro-1H-indazol-3-yl)-[8-methoxy-2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-92)*): Prepared using THF as solvent to afford the title compound as a TFA salt (98 mg, 58% yield). HPLC-Method A, R_t 3.20 min (92%); $^1\text{HNMR}$ (DMSO-d₆, 500 MHz) δ 13.45 (1H, bs), 11.0 - 10.7 (1H, bs), 8.25 (1H, m), 7.75-7.60 (5H, m), 7.50 (1H, m), 7.40 (1H, m), 7.15 (1H, m), 6.95 (1H, m) 4.0 (3H, s); MS (m/z) 454.2 (M+H).

Example 93 (*5,7-Difluoro-1H-indazol-3-yl)-[8-methoxy-2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-93)*): Prepared using THF as solvent to afford the title compound as a TFA salt (36% yield). HPLC-Method A, R_t 3.27 min. (95%); $^1\text{HNMR}$ (DMSO-d₆, 500 MHz): 13.65 (1H, bs), 11.0 - 10.7 (1H, bs), 8.22 (1H, m), 7.75-7.60 (5H, m),

7.40 (1H, m), 7.35 (1H, m), 7.19 (1H, m), 4.0 (3H, s); MS (m/z) 472.2 (M+H).

Example 94 [2-(2-Chloro-pyridin-3-yl)-quinazolin-4-yl]-
5 (5,7-Difluoro-1*H*-indazol-3-yl)-amine (II-94): Prepared in
DMF. $^1\text{HNMR}$ (500MHz, DMSO-d6) δ 13.62 (br s, 1H, 11.06-
10.71 (m, 1H), 8.16-7.70 (m, 4H), 7.60-7.09 (m, 3H); LC-
MS (ES+) 409.14 (M+H); HPLC-Method A, R_t 2.89 min.

10 Example 95 [2-(2-Chloro-4-nitro-phenyl)-quinazolin-4-yl]-
(5,7-difluoro-1*H*-indazol-3-yl)-amine (II-95): Prepared in
THF. $^1\text{HNMR}$ (500MHz, DMSO-d6) δ 13.35 (s, 1H), 10.74 (s,
1H), 8.67 (d, $J=8.4\text{Hz}$, 1H), 8.29 (d, $J=2.05\text{Hz}$, 1H), 8.18-
8.08 (m, 1H), 8.07-7.60 (m, 4H), 7.53-7.10 (m, 2H). LC-
15 MS (ES+) 453.15 (M+H); HPLC-Method D, R_t 3.63 min.

Example 96 [2-(4-Amino-2-chloro-phenyl)-quinazolin-4-yl]-
(5,7-Difluoro-1*H*-indazol-3-yl)-amine (II-96):
A solution of compound II-95 (8mg, 0.018mmol) and tin
20 chloride dihydrate (22mg, 0.1mmol) in ethanol (2mL) was
heated at 100°C for 24h. The reaction was diluted with
EtOAc (10mL), washed with 1N NaOH solution (2x10mL),
brine, and dried over anhydrous sodium sulfate to afford
the crude product. Purification was achieved by flash
25 chromatography on silica gel (eluting with 1-3% MeOH in
 CH_2Cl_2 .) The title compound was isolated as pale yellow
solid (1.2mg, 16% yield). LC-MS (ES+) 423.12 (M+H),
HPLC-Method C, R_t 13.78 min.

30 Example 97 (4,5,6,7-Tetrahydro-1*H*-indazol-3-yl)
- [2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine
(II-97): Prepared in 34% yield. $^1\text{HNMR}$ (500MHz, DMSO-d6) δ
1.58 (m, 2H), 1.66 (m, 2H), 2.24 (m, 2H), 2.54 (m 2H),

7.63 (m, 3H), 7.71 (t, 1H), 7.75 (d, 1H), 7.78 (d, 1H),
7.85 (t, 1H), 8.53 (d, 1H), 9.99 (s, 1H), 12.09 (s, 1H);
EI-MS 410.2 (M+1); HPLC-Method A, R_t 3.05 min.

5 Example 98 (*1H-Pyrazolo[4,3-b]pyridin-3-yl*)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-98):
Prepared in DMF (37% yield) as yellow solid. ¹HNMR (500 MHz, DMSO-d6) δ 13.1 (s, br, 1H), 11.2 (s, br, 1H), 8.73
10 (d, 1H), 8.54 (dd, 1H), 8.12 (d, 1H), 8.06 (t, 1H), 7.90 (d, 1H), 7.84 (t, 1H), 7.75 (d, 1H), 7.69 (m, 2H), 7.65
(t, 1H), 7.47 (dd, 1H) ppm; LC-MS (ES+) 407.18 (M+H);
HPLC-Method A, R_t 2.77 min.

15 Example 99 (*1H-Pyrazolo[3,4-b]pyridin-3-yl*)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-99):
Prepared in DMF (45% yield). ¹HNMR (500 MHz, DMSO-d6)
δ 13.5 (s, br, 1H), 11.3 (s, br, 1H), 8.78 (d, 1H), 8.49
(d, 1H), 8.17 (d, 1H), 8.03 (t, 1H), 7.89 (d, 1H), 7.80
(m, 2H), 7.74 (m, 2H), 7.68 (m, 1H), 7.08 (dd, 1H) ppm.
20 MS (ES+) 407.16 (M+H), (ES-) 405.16 (M-H); HPLC-Method A,
R_t 2.80 min.

25 Example 100 (*6-Methyl-1H-pyrazolo[3,4-b]pyridin-3-yl*)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-100): Prepared in DMF (11% yield). ¹HNMR (500 MHz, DMSO-d6) δ 13.2 (s, br, 1H), 10.8 (s, br, 1H), 8.57 (d, 1H),
7.95 (t, 1H), 7.82 (d, 1H), 7.72 (t, 1H), 7.65 (m, 2H),
7.58 (m, 2H), 2.44 (s, 3H, buried by DMSO), 2.20 (s, 3H)
ppm. LC-MS (ES+) 435.22 (M+H), (ES-) 433.25 (M-H); HPLC-
30 Method A, R_t 2.94 min.

Example 101 (*6-Oxo-5-phenyl-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl*)-[2-(2-trifluoromethyl-phenyl)-

quinazolin-4-yl]-amine II-101: Prepared in DMF (6% yield). ^1H NMR (500 MHz, DMSO-d₆) δ 12.6 (s, 1H), 11.0 (s, br, 1H), 8.60 (d, 1H), 7.95 (t, 1H), 7.88 (d, 1H), 7.80 (d, 1H), 7.68 (m, 4H), 7.40 (s, 3H), 7.22 (s, 2H), 6.61 (s, 1H) ppm. LC-MS (ES+) 500.21 (M+H), (ES-) 498.16 (M-H); HPLC-Method A, R_t 3.00 min.

Example 103 [6-Methyl-2-(2-trifluoromethoxy-phenyl)-pyrimidin-4-yl]-(5-phenyl-2H-pyrazol-3-yl)-amine (II-103): MS 412.13 (M+H); HPLC-Method E R_t 1.248 min.

Example 104 (5-Furan-2-yl-2H-pyrazol-3-yl)-[6-methyl-2-(2-trifluoromethoxy-phenyl)-pyrimidin-4-yl]-amine (II-104); MS 402.12 (M+H); HPLC-Method E, R_t 1.188 min.

Example 105 [6-Ethyl-2-(2-trifluoromethoxy-phenyl)-pyrimidin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (II-105): MS 364.14 (M+H); HPLC-Method E, R_t 1.112 min.

Example 106 [2-(2-Chloro-phenyl)-pyrido[2,3-d]pyrimidin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (II-106): ^1H NMR (500 MHz, DMSO) δ 12.23 (s, 1H), 10.78 (s, 1H), 7.73-7.47 (m, 7H), 6.72 (s, 1H), 2.21 (s, 3H). MS: (M+H) 337.02. HPLC-Method A, R_t 2.783 min.

Example 107 (5-Fluoro-1H-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-yl]-amine (II-107): Prepared in 68% yield. ^1H NMR (500MHz, DMSO-d₆) δ 2.16 (t, 2H), 2.88 (m, 2H), 2.98 (t, 2H), 7.21 (td, 1H), 7.29 (dd, 1H), 7.50 (dd, 1H), 7.65 (t, 1H), 7.67 (t, 1H), 7.73 (t, 1H), 7.79 (d, 1H), 10.22 (br. s, 1H), 12.99 (br. s, 1H); EI-MS 414.2 (M+H); HPLC-Method A, R_t 2.92 min.

Example 108 (*1H-Indazol-3-yl*) - [2- (2-trifluoromethyl-phenyl) -pyrido[2,3-d]pyrimidin-4-yl] -amine (II-108) :
HPLC-Method A, R_t 2.78 min. (95%) ; ¹HNMR (DMSO-d6, 500 MHz) : 12.95 (1H, bs), 11.45 δ 11.15(1H, bs), 9.20 (2H, m), 7.85-7.70 (2H, m), 7.70-7.55 (4H, m), 7.50 (1H, m), 7.35 (1H, m), 7.05 (1H, m); MS (m/z) 407.03 (M+H).

Example 109 (5,7-Difluoro-*1H-indazol-3-yl*) - [2- (2-trifluoromethyl-phenyl) -pyrido[2,3-d]pyrimidin-4-yl] -amine (II-109) : Yellow, di-TFA salt (25% yield). HPLC (Method A) 3.10 min. (95%) ; ¹HNMR (DMSO-d6, 500 MHz) : 13.8-13.6 (1H, bs), 11.4 - 11.2(1H, bs), 9.15 (2H, m), 7.85-7.75 (2H, m), 7.75-7.62 (3H, m), 7.32 (2H, m); MS (m/z) 442.98 (M+H).

Example 110 [2- (2-Chloro-phenyl) -pyrido[2,3-d]pyrimidin-4-yl] - (*1H-indazol-3-yl*) -amine (II-110) : Prepared from 2-aminonicotinic acid and 2-chlorobenzoyl chloride afforded the title compound as a di-TFA salt (28% yield). HPLC-Method A, R_t 2.85 min. (95%) ; ¹HNMR (DMSO-d6, 500 MHz) : 12.90 (1H, s), 11.10 - 10.90 (1H, bs), 9.05 (2H, m), 7.75-7.60 (2H, m), 7.51 (1H, m), 7.45-7.25 (5H, m), 6.95 (1H, m); MS (m/z) 372.99 (M+H).

Example 111 (5-Fluoro-*1H-indazol-3-yl*) - [2- (2-trifluoromethyl-phenyl) -5,6,7,8,9,10-hexahydro-cyclooctapyrimidin-4-yl] -amine (II-111) . Prepared in 43% yield. ¹HNMR (500MHz, DMSO-d6) δ 1.46 (m, 2H), 1.53 (m, 2H), 1.77 (m, 4H), 2.95 (m, 2H), 3.04 (m, 2H), 7.22 (m, 2H), 7.50 (dd, 1H), 7.72 (m, 3H), 7.80 (d, 1H), 10.5 (m, 1H), 13.05 (br s, 1H); EI-MS 456.2 (M+H) ; HPLC-Method C, R_t 11.93 min.

Example 112 [2-(2-Chloro-phenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-yl]- (5-fluoro-1H-indazol-3-yl)-amine (II-112): Prepared in 67% yield. $^1\text{HNMR}$ (500MHz, DMSO-d6) δ 2.18 (m, 2H), 2.89 (m, 2H), 3.02 (t, 2H), 7.24 (td, 1H), 7.42 (m, 2H), 7.49 (td, 1H), 7.52 (dd, 1H), 7.54 (d, 1H), 7.57 (dd, 1H), 10.50 (br. s, 1H), 13.06 (br. s, 1H); EI-MS 380.1 (M+1); HPLC-Method C, R_t 9.68 min.

10

Example 113 (1H-Indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-yl]-amine (II-113): Prepared in 37% yield. $^1\text{HNMR}$ (500MHz, DMSO-d6) δ 2.65 (m, 2H), 2.85 (m, 2H), 2.99 (t, 2H), 7.02 (t, 1H), 7.32 (t, 1H), 7.47 (d, 1H), 7.55 (d, 1H), 7.68 (t, 1H), 7.74 (t, 1H), 7.80 (d, 1H), 10.37 (br. s, 1H), 12.91 (br. s, 1H); EI-MS 396.1 (M+H); HPLC-Method B, R_t 9.88 min.

20

Example 114 (7-Fluoro-1H-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-yl]-amine (II-114): Prepared in 40% yield. $^1\text{HNMR}$ (500MHz, DMSO-d6) δ 2.15 (m, 2H), 2.87 (m, 2H), 2.97 (t, 2H), 6.99 (td, 1H), 7.17 (dd, 1H), 7.38 (d, 1H), 7.65 (m, 2H), 7.71 (t, 1H), 7.78 (d, 1H), 10.21 (br. s, 1H), 13.40 (br. s, 1H); EI-MS 414.1 (M+H); HPLC-Method C, R_t 9.99 min.

30

Example 115 (5,7-Difluoro-1H-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-yl]-amine (II-115): Prepared according to Method C in 52% yield. $^1\text{HNMR}$ (500MHz, DMSO-d6) δ 2.16 (m, 2H), 2.89 (m, 2H), 2.97 (t, 2H), 7.19 (dd, 1H), 7.29 (td, 1H), 7.63 (t, 1H), 7.66 (d, 1H), 7.71 (t,

1H), 7.78 (d, 1H), 10.16 (br. s, 1H), 13.55 (br. s, 1H);
EI-MS 432.1 (M+H); HPLC-Method C, R_t 10.09 min.

Example 116 [2-(2-Chloro-phenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-yl]- (1H-indazol-3-yl)-amine (II-116): Prepared in 56% yield. ¹HNMR (500MHz, DMSO-d6) δ 2.16 (m, 2H), 2.85 (m, 2H), 3.01 (t, 2H), 7.06 (t, 1H), 7.34 (t, 1H), 7.40 (t, 1H), 7.48 (m, 2H), 7.53 (d, 1H), 7.56 (d, 1H), 7.63 (d, 1H), 10.39 (br. s, 1H), 12.91 (s, 1H); EI-MS 362.1 (M+H); HPLC-Method A, R_t 3.09 min.

Example 117 [2-(2-Chloro-phenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-yl]- (7-fluoro-1H-indazol-3-yl)-amine (II-117): Prepared in 63% yield. ¹HNMR (500MHz, DMSO-d6) δ 2.15 (m, 2H), 2.87 (m, 2H), 3.00 (t, 2H), 7.01 (td, 1H), 7.19 (dd, 1H), 7.39 (t, 1H), 7.45 (m, 2H), 7.51 (d, 1H), 7.55 (d, 1H), 10.35 (br. s, 1H), 13.45 (br. s, 1H); EI-MS 380.1 (M+H); HPLC-Method A, R_t 3.15 min.

Example 118 [2-(2-Chloro-phenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-yl]- (5,7-difluoro-1H-indazol-3-yl)-amine (II-118): Prepared in 60% yield. ¹HNMR (500MHz, DMSO-d6) δ 2.18 (m, 2H), 2.91 (m, 2H), 3.01 (t, 2H), 7.32 (t, 1H), 7.33 (td, 1H), 7.41 (t, 1H), 7.48 (t, 1H), 7.53 (d, 1H), 7.55 (dd, 1H), 10.35 (br. s, 1H), 13.45 (br. s, 1H); EI-MS 398.1 (M+H); HPLC-Method A, R_t 3.24 min.

Example 119 (1H-Indazol-3-yl)- [2-(2-trifluoromethyl-phenyl)-5,6,7,8,9,10-hexahydro-cyclooctapyrimidin-4-yl]-amine (II-119): Prepared in 36% yield. ¹HNMR (500MHz, DMSO-d6) δ 1.47 (m, 2H), 1.53 (m, 2H), 1.78 (m, 4H), 2.96 (m, 2H), 3.06 (t, 2H), 7.03 (t, 1H), 7.47 (t, 1H), 7.72 (d, 1H), 7.73 (d, 1H), 7.72 (m, 3H), 7.81 (d, 1H), 10.52

(m, 1H), 12.97 (br. s, 1H); EI-MS 438.2 (M+1); HPLC-
Method A, R_t 3.37 min.

Example 120 (7-Fluoro-1H-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-5,6,7,8,9,10-hexahydro-cyclooctapyrimidin-4-yl]-amine (II-120): Prepared in 40% yield. ¹H NMR (500MHz, DMSO-d6) δ 1.46 (m, 2H), 1.52 (m, 2H), 1.77 (m, 4H), 2.94 (m, 2H), 3.04 (m, 2H), 7.00 (td, 1H), 7.17 (dd, 1H), 7.30 (d, 1H), 7.70 (m, 3H), 7.79 (d, 1H), 10.5 (m, 1H), 13.49 (br s, 1H); EI-MS 456.1 (M+H); HPLC-Method A, R_t 3.43 min.

Example 121 (5,7-Difluoro-1H-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-5,6,7,8,9,10-hexahydro-cyclooctapyrimidin-4-yl]-amine (II-121): Prepared in 48% yield. ¹H NMR (500MHz, DMSO-d6) δ 1.46 (m, 2H), 1.52 (m, 2H), 1.77 (m, 4H), 2.95 (m, 2H), 3.03 (m, 2H), 7.14 (d, 1H), 7.30 (t, 1H), 7.73 (m, 3H), 7.80 (d, 1H), 10.5 (m, 1H), 13.62 (br. s, 1H); EI-MS 475.1 (M+1); HPLC-Method A, R_t 3.52 min.

Example 122 [6-Cyclohexyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]- (1H-indazol-3-yl)-amine (II-122): Prepared in 45% yield. ¹H NMR (500 MHz, CDCl₃) δ 1.30 (2H, m), 1.46 (2H, m), 1.65 (2H, m), 1.76 (2H, m), 1.91 (2H, m), 2.61 (1H, br m), 7.08 (1H, t, J=7.4 Hz), 7.27 (1H, d, J=8.0 Hz), 7.35 (1H, t, J= 7.1 Hz), 7.50 (1H, t, J=7.0 Hz), 7.58 (1H, t, J=7.4 Hz), 7.66 (3H, m), 7.72 (1H, d, J=7.8 Hz), 8.0 (1H, br), 9.87 (1H, br) ppm; HPLC-Method D, R_t 3.57 min; LC-MS 438.17 (M+H)⁺

Example 123 [6-(2-Fluoro-phenyl)-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]- (1H-indazol-3-yl)-amine (II-123):

Prepared in 8% yield. ^1H NMR (500 MHz, CDCl_3) δ 7.18 (3H, m), 7.37 (1H, m), 7.43 (1H, t, $J=7.9$ Hz), 7.51 (1H, d, $J=7.9$ Hz), 7.55 (1H, t, $J=7.6$ Hz), 7.65 (1H, t, $J=7.4$ Hz), 7.79 (1H, d, $J=7.9$ Hz), 7.85 (1H, d, $J=7.6$ Hz),
5 8.19 (2H, m), 8.70 (1H, d, $J=8.5$ Hz) ppm; HPLC-Method D,
 R_t 4.93 min; LC-MS 450.13 ($M+H$)⁺

Example 124 (6-Fluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-amine (II-124):
10 Prepared in DMF (87% yield) as yellow solid. ^1H NMR (500 MHz, DMSO-d_6) δ 13.0 (s, 1H), 11.1 (s, br, 1H), 8.66 (d, 1H), 7.95 (t, 1H), 7.80 (d, 1H), 7.72 (m, 2H), 7.62 (m, 4H), 7.21 (dd, 1H), 6.84 (td, 1H) ppm. LC-MS (ES+) 424.15 ($M+H$); HPLC-Method A, R_t 3.05 min.
15
Example 125 3-[2-(2-Trifluoromethyl-phenyl)-quinazolin-4-ylamino]-1*H*-indazole-5-carboxylic acid methyl ester (II-125): To a solution of compound II-79 (100 mg 0.21 mmol) in DMF (2 mL) was added MeOH (1 mL), DIEA (54 μL , 0.31 mmol) and $\text{PdCl}_2(\text{dppf})$ (4 mg, 0.005 mmol). The flask was flushed with CO three times and then charged with a CO balloon. The reaction mixture was heated at 80°C for 14 h then poured into water. The resulting precipitate was collected and washed with water. The crude product was 20 then purified first by flash column (silica gel, 50% ethyl acetate in hexanes) then by preparative HPLC to afford II-125 (32%) as yellow solid. ^1H NMR (500 MHz, DMSO-d_6) δ 13.3 (s, 1H), 11.3 (s, br, 1H), 8.70 (d, 1H), 8.36 (s, 1H), 7.97 (t, 1H), 7.82 (m, 2H), 7.71 (m, 3H), 25 7.58 (m, 2H), 7.51 (d, 1H), 3.75 (s, 3H) ppm; LC-MS (ES+) 464.13 ($M+H$); HPLC-Method A, R_t 3.12 min.
30

Example 208 (5-Methyl-2H-pyrazol-3-yl)-[2-(2-naphthyl-1-yl)-quinazolin-4-yl]-amine (II-208): ^1H NMR (500 MHz, DMSO-d₆) δ 8.92 (s, 1H), 8.73 (m, 1H), 8.39 (m, 1H), 8.09 (m, 2H), 7.95 (m, 3H), 7.62 (m, 3H), 6.78 (s, 1H), 2.32 (s, 5 3H); MS 352.2 (M+H).

Example 209 [2-(2-Chloro-phenyl)-pyrido[2,3-d]pyrimidin-4-yl]- (7-fluoro-1H-indazol-3-yl)-amine (II-214): Prepared from 4-Chloro-2-(2-chloro-phenyl)-pyrido[2,3-d]pyrimidine (100 mg, 0.36mmol) and 7-Fluoro-1H-indazol-3-ylamine (108mg, 0.72mmol). Purification by preparative HPLC afforded the title compound as a yellow, di-TFA salt (93 mg, 46% yield). HPLC-Method A, R_t 3.04 min; ^1H .NMR (DMSO, 500 MHz): δ 13.67 (1H, s), 11.40-11.25 (1H, bs), 9.35-10 9.25 (2H, m), 7.95 (1H, m), 7.80-7.47 (5H, m), 7.35(1H, m), 7.15 (1H, m); MS (m/z), MH⁺ 391.1.

Example 210 [2-(2-Chloro-phenyl)-pyrido[2,3-d]pyrimidin-4-yl]- (5-fluoro-1H-indazol-3-yl)-amine (II-215): Prepared from 4-Chloro-2-(2-chloro-phenyl)-pyrido[2,3-d]pyrimidine (100 mg, 0.36mmol) and 5-Fluoro-1H-indazol-3-ylamine (108mg, 0.72mmol). Purification by preparative HPLC afforded the title compound as a yellow, di-TFA salt (45 mg, 22% yield). HPLC-Method A, R_t 3.00 min; ^1H NMR (DMSO, 500 MHz): δ 13.0 (1H, s), 10.90(1H, bs), 9.15-9.05 25 (2H, m), 7.70 (1H, m), 7.60-7.30 (6H, m), 7.20 (1H, m); MS (m/z), MH⁺ 391.1.

Example 211 [2-(2-Chloro-phenyl)-pyrido[2,3-d]pyrimidin-4-yl]- (5,7-difluoro-1H-indazol-3-yl)-amine (II-216): Prepared from 4-Chloro-2-(2-chloro-phenyl)-pyrido[2,3-d]pyrimidine (100 mg, 0.36mmol) and 7-Difluoro-1H-indazol-3-ylamine (112mg, 0.66mmol). Purification by

preparative HPLC afforded the title compound as a yellow, di-TFA salt (130 mg, 62% yield). HPLC-Method A, R_t 3.12 min; ^1H NMR (DMSO, 500 MHz): 13.80-13.60 (1H, bs), 11.30-11.10 (1H, bs), 9.20-9.10 (2H, m), 7.80 (1H, m), 7.60-7.30 (6H, m); MS (m/z), MH^+ 409.1.

5 Example 212 [2-(2-Chloro-phenyl)-pyrido[3,4-d]pyrimidin-4-yl]- (1*H*-indazol-3-yl)-amine (II-217): Prepared from 4-Chloro-2-(2-chloro-phenyl)-pyrido[3,4-d]pyrimidine (100 mg, 0.36mmol) and 1*H*-indazol-3-ylamine (88mg, 0.66mmol) 10 Purification by preparative HPLC afforded the title compound as a yellow, di-TFA salt (72 mg, 33% yield). HPLC-Method A, R_t 3.21 min; ^1H NMR (DMSO, 500 MHz): δ 12.95 (1H, s), 10.90 (1H, bs), 9.25 (1H, s), 8.75 (1H, m), 8.55 (1H, m), 7.65 (1H, m), 7.55 (1H, m), 7.50-7.30 (5H, m), 7.00(1H, m); MS (m/z), MH^+ 373.1.

15 Example 213 [2-(2-Chloro-phenyl)-pyrido[3,4-d]pyrimidin-4-yl]- (7-fluoro-1*H*-indazol-3-yl)-amine (II-218): Prepared 20 from 4-Chloro-2-(2-chloro-phenyl)-pyrido[3,4-d]pyrimidine (100 mg, 0.36mmol) and 7-Fluoro-1*H*-indazol-3-ylamine (108mg, 0.72mmol). Purification by preparative HPLC afforded the title compound as a yellow, di-TFA salt (48.7 mg, 22% yield). HPLC-Method A, R_t 3.35 min; ^1H NMR 25 (DMSO, 500 MHz): δ 12.95 (1H, s), 10.90 (1H, bs), 9.25 (1H, s), 8.75 (1H, m), 8.55 (1H, m), 7.70-7.35 (5H, m), 7.25(1H, m), 6.95 (1H, m), ; MS (m/z), MH^+ 391.08.

30 Example 214 [2-(2-Chloro-phenyl)-pyrido[3,4-d]pyrimidin-4-yl]- (5-fluoro-1*H*-indazol-3-yl)-amine (II-219): Prepared from 4-chloro-2-(2-chloro-5-fluoro-1*H*-indazol-3-ylamine (108mg, 0.72mmol). Purification by preparative HPLC. afforded the title compound as a yellow, di-TFA salt

(57.2 mg, 26% yield). HPLC-Method A, R_t 3.27 min; ¹H NMR (DMSO, 500 MHz): δ 13.05 (1H, s), 10.95 (1H, s), 9.25 (1H, s), 8.75 (1H, m), 8.55 (1H, m), 7.60 (1H, m), 7.55 (1H, m), 7.50-7.30 (5H, m), 7.25 (1H, m); MS (m/z), MH⁺ 5 391.1.

Example 215 [2-(2-Chloro-phenyl)-pyrido[3,4-d]pyrimidin-4-yl]- (5,7-difluoro-1H-indazol-3-yl)-amine (II-220): Prepared from 4-chloro-2-(2-chloro-7-difluoro-1H-indazol-10 3-yl)amine (112mg, 0.66mmol). Purification by preparative HPLC afforded the title compound as a yellow, di-TFA salt (57.2 mg, 26% yield). HPLC-Method A, R_t 3.45 min; ¹H NMR (DMSO, 500 MHz): δ 13.65 (1H, s), 11.0 (1H, s), 9.25 (1H, s), 8.80 (1H, m), 8.50 (1H, m), 7.60 (1H, m), 7.55 (1H, m), 7.50-7.30 (5H, m); MS (m/z), MH⁺ 409.1.

Example 216 6-Fluoro-1H-indazol-3-ylamine (A1): ¹HNMR (500 MHz, DMSO-d6) δ 11.4 (s, 1H), 7.68 (dd, 1H), 6.95 (dd, 1H), 6.75 (td, 1H), 5.45 (s, 2H) ppm; LC-MS (ES+) 20 152.03 (M+H); HPLC-Method A, R_t 2.00 min.

Example 217 5-Fluoro-1H-indazol-3-ylamine (A2): ¹HNMR (500 MHz, DMSO-d6) δ 11.3 (s, 1H), 7.43 (d, 1H), 7.22 (m, 1H), 7.08 (m, 1H), 5.29 (s, 2H) ppm; LC-MS (ES+) 152.01 25 (M+H); HPLC-Method A, R_t 1.93 min.

Example 218 5,7-Difluoro-1H-indazol-3-yl-amine (A3): ¹HNMR (500 MHz, CD₃OD) δ 7.22 (dd, J=2.0, 8.45Hz, 1H), 7.04-6.87 (m, 1H); LC-MS (ES+) 169.95 (M+H); HPLC-Method C, R_t 2.94 30 min

Example 219 7-Fluoro-1H-indazol-3-ylamine (A4): ¹HNMR (500 MHz, DMSO-d6) δ 11.8 (s, 1H), 7.42 (d, 1H), 6.97 (m, 1H),

6.78 (m, 1H), 5.40 (s, 2H) ppm; LCMS (ES+) 152.01 (M+H);
HPLC-Method A, R_t 2.00 min.

Example 220 7-Fluoro-6-trifluoromethyl-1*H*-indazol-3-

5 **ylamine (A5):** ¹H-NMR (500 MHz, DMSO) δ 12.5 (s, 1H), 7.75
(d, 1H), 7.25 (m, 1H), 5.85 (m, 1H) ppm; MS (FIA) 220.0
(M+H); HPLC-Method A, R_t 2.899 min.

Example 221 6-Bromo-1*H*-indazol-3-ylamine (A6): ¹H-NMR (500

10 MHz, DMSO) δ 11.5 (s, 1H), 7.65 (d, 1H), 7.40 (s, 1H),
7.00 (d, 1H), 5.45 (br s, 1H) ppm; MS (FIA) 213.8 (M+H);
HPLC-Method A, R_t 2.441 min.

Example 222 4-Fluoro-1*H*-indazol-3-ylamine (A7): ¹H-NMR

15 (500 MHz, DMSO) δ 11.7 (s, 1H), 7.17 (m, 1H), 7.05 (d,
1H), 6.7 (br, 1H), 6.60 (dd, 1H), 5.20 (br s, 2H) ppm; MS
(FIA) 152.0 (M+H); Method A, R_t 2.256 min.

Example 223 5-Bromo-1*H*-indazol-3-ylamine (A8): ¹H-NMR (500

20 MHz, DMSO) δ 11.55 (br s, 1H), 7.95 (s, 1H), 7.30 (d,
1H), 7.20 (d, 1H), 5.45 (br s, 2H) ppm; MS (FIA) 213.8
(M+H); Method A, R_t 2.451 min.

Example 224 5-Nitro-1*H*-indazol-3-ylamine (A9): ¹H-NMR (500

25 MHz, DMSO-d6) δ 9.00 (s, 1H), 8.20 (d, 1H), 7.45 (d, 1H),
6.15 (br s, 1H) ppm; Method A, R_t 2.184 min

Example 225 4-Pyrrol-1-yl-1*H*-indazol-3-ylamine (A10): ¹H-

NMR (500 MHz, DMSO) δ 7.20 (s, 2H), 7.00 (s, 2H), 6.75
30 (m, 1H), 6.25 (s, 2H), 4.30 (d, 1H) ppm; Method A, R_t
2.625 min.

Example 226 4-Chloro-5,6-dimethyl-2-(2-trifluoromethyl-phenyl)-pyrimidine (B1): Prepared to afford a colorless oil in 75% yield. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.70 (d, $J=7.8$ Hz, 1H), 7.64 (d, $J=7.6$ Hz, 1H), 7.55 (t, $J=7.6$ Hz, 1H), 7.48 (t, $J=7.5$ Hz, 1H), 2.54 (s, 3H), 2.36 (s, 3H) ppm; MS (FIA) 287.0 ($M+H$); HPLC-Method A, R_t 3.891 min.

Example 227 4-Chloro-2-(2-chloro-phenyl)-5,6-dimethyl-pyrimidine (B2): Prepared to afford a yellow-orange oil in 71% yield. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.73 (m, 1H), 7.52 (m, 1H), 7.39 (m, 2H), 2.66 (s, 3H), 2.45 (s, 3H) ppm; MS (FIA) 253.0 ($M+H$); HPLC-Method A, R_t 4.156 min.

Example 228 4-Chloro-6-methyl-2-(2-trifluoromethyl-phenyl)-pyrimidine (B3): Prepared to afford a pale yellow oil in 68% yield. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.72 (d, $J=7.8$ Hz, 1H), 7.65 (d, $J=7.9$ Hz, 1H), 7.57 (t, $J=7.5$ Hz, 1H), 7.52 (t, $J=7.8$ Hz, 1H), 7.16 (s, 1H), 2.54 (s, 3H) ppm; MS (FIA) 273.0 ($M+H$); HPLC-Method A, R_t 3.746 min.

Example 229 4-Chloro-6-cyclohexyl-2-(2-trifluoromethyl-phenyl)-pyrimidine (B4): Prepared to afford a yellow oil in 22% yield. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.70 (m, 2H), 7.57 (t, $J=7.5$ Hz, 1H), 7.50 (t, $J=7.5$ Hz, 1H), 7.19 (s, 1H), 2.65 (m, 1H), 1.9 (m, 2H), 1.8 (m, 2H), 1.5 (m, 2H), 1.3 (m, 2H), 1.2 (m, 2H) ppm; MS (FIA) 341.0 ($M+H$).

Example 230 4-Chloro-6-phenyl-2-(2-trifluoromethyl-phenyl)-pyrimidine (B5): Prepared to afford a yellow oil in 53% yield. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 8.08 (dd, $J=7.9$, 1.6 Hz, 2H), 7.80 (d, $J=7.6$ Hz, 1H), 7.77 (d, $J=7.8$ Hz, 1H), 7.67 (s, 1H), 7.61 (t, $J=7.5$ Hz, 1H), 7.54 (t, $J=7.6$

Hz, 1H), 7.47 (m, 3H) ppm; MS (FIA) 335.0 (M+H); HPLC-Method A, R_t 4.393 min.

Example 231 4-Chloro-2-(2,4-dichloro-phenyl)-5,6-dimethyl-pyrimidine (B6): Prepared to afford a white solid in 91% yield. ¹H-NMR (500 MHz, CDCl₃) δ 7.62 (d, J=8.3 Hz, 1H), 7.43 (d, J=7.0 Hz, 1H), 7.27 (dd, J=8.3, 2.0 Hz, 1H), 2.55 (s, 3H), 2.35 (s, 3H) ppm; MS (FIA) 287, 289 (M+H); HPLC-Method A, R_t 4.140 min.

10

Example 232 4-Chloro-6-(2-chloro-phenyl)-2-(2-trifluoromethyl-phenyl)-pyrimidine (B7): Prepared to afford a yellow oil in 52% yield. ¹H-NMR (500 MHz, CDCl₃) δ 7.75 (m, 3H), 7.65 (m, 2H), 7.53 (m, 1H), 7.44 (m, 1H), 7.36 (m, 2H) ppm; MS (FIA) 369.1 (M+H); HPLC-Method A, R_t 4.426 min.

Example 233 4-Chloro-6-(2-fluoro-phenyl)-2-(2-trifluoromethyl-phenyl)-pyrimidine (B8): Prepared to afford a yellow oil in 95% yield. ¹H-NMR (500 MHz, CDCl₃) δ 8.24 (t, J=7.9 Hz, 1H), 7.84 (s, 1H), 7.78 (d, J=7.7 Hz, 1H), 7.76 (d, J=8.0 Hz, 1H), 7.60 (t, J=7.5 Hz, 1H), 7.53 (t, J=7.6 Hz, 1H), 7.43 (m, 1H), 7.23 (t, J=7.6 Hz, 1H), 7.13 (m, 1H) ppm; MS (FIA) 353.0 (M+H).

25

Example 234 4-Chloro-6-pyridin-2-yl-2-(2-trifluoromethyl-phenyl)-pyrimidine (B9): Prepared to afford a pale yellow solid in 50% yield. ¹H-NMR (500 MHz, CDCl₃) δ 8.68 (m, 1H), 8.48 (dd, J=7.9, 0.8 Hz, 1H), 8.38 (d, J=2.3 Hz, 1H), 7.84 (m, 3H), 7.62 (t, J=7.6 Hz, 1H), 7.55 (t, J=7.6 Hz, 1H), 7.38 (m, 1H) ppm; MS (FIA) 336.0 (M+H); HPLC-Method A, R_t 4.575 min.

Example 235 6-Benzyl-4-chloro-2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine (B10):
¹HNMR (500 MHz, CDCl₃) δ 7.70 (d, 1H), 7.62 (d, 1H), 7.55 (t, 1H), 7.48 (t, 1H), 7.32 (m, 4H), 7.25 (m, 1H), 3.74 (s, 2H), 3.66 (s, 2H), 2.99 (t, 2H), 2.80 (t, 2H) ppm;
LCMS (ES+) 404.17 (M+H); HPLC-Method A, R_t 3.18 min.

Example 236 7-Benzyl-4-chloro-2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine (B11):
10 ¹HNMR (500 MHz, CDCl₃) δ 7.69 (d, 1H), 7.60 (d, 1H), 7.54 (t, 1H), 7.47 (t, 1H), 7.28 (m, 4H), 7.20 (m, 1H), 3.68 (s, 2H), 3.67 (s, 2H), 2.86 (t, 2H), 2.79 (t, 2H) ppm. MS (ES+) 404.18 (M+H); HPLC-Method A, R_t 3.12 min.

15 Example 237 4-Chloro-2-(4-fluoro-2-trifluoromethyl-phenyl)-quinazoline (B12): ¹HNMR (500MHz, CD₃OD) δ 8.43 (d, J=8.1Hz, 1H), 8.20-8.05 (m, 2H), 8.05-7.82 (m, 2H), 7.71-7.51 (m, 2H). LC-MS (ES+) 327.09 (M+H). HPLC-Method D, R_t 4.56 min.

20 Example 238 4-Chloro-2-(2-chloro-5-trifluoromethyl-phenyl)-quinazoline (B13): LC-MS (ES+) 342.97 (M+H). HPLC-Method D, R_t 4.91 min.

25 Example 239 4-Chloro-2-(2-chloro-4-nitro-phenyl)-quinazoline (B14): LC-MS (ES+) 319.98 (M+H). HPLC-Method D, R_t 4.45 min.

30 Example 240 4-Chloro-2-(2-trifluoromethyl-phenyl)-quinazoline (B15): Prepared in 57% yield. White solid.
¹HNMR (500MHz, DMSO-d6) δ 7.79 (t, 1H), 7.86 (t, 1H), 7.94 (m, 3H), 8.15 (dd, 1H), 8.20 (td, 1H), 8.37 (m, 1H); EI-MS 308.9 (M).

Example 241 4-Chloro-2-(2-trifluoromethyl-phenyl)-6,7-dihydro-5H-cyclopentapyrimidine (B16): Prepared in 22% yield. $^1\text{HNMR}$ (500MHz, DMSO-d₆) δ 2.19 (m, H), 3.01 (t, 2H), 3.08 (t, 2H), 7.49 (t, 1H), 7.55 (t, 1H), 7.62 (d, 1H), 7.71 (d, 1H). EI-MS 299.0 (M+H).

Example 242 4-Chloro-2-(2-chloro-phenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyrimidine (B17): Prepared according to Method C in 82% yield to afford a white solid. $^1\text{HNMR}$ (500MHz, CDCl₃) δ 1.67 (m 4H), 1.87 (m 2H), 3.02 (m 4H), 7.28 (m, 2H), 7.40 (m, 1H), 7.65 (m, 1H); EI-MS 293.0 (M+1).

Example 243 4-Chloro-2-(2-trifluoromethyl-phenyl)-5,6,7,8,9,10-hexahydro-cyclooctapyrimidine (B18): Prepared in 38% yield to afford a brown oil. $^1\text{HNMR}$ (500MHz, CDCl₃) δ 1.35 (m 2H), 1.41 (m 2H), 1.76 (m 4H), 2.96 (m, 4H), 7.48 (t, 1H), 7.56 (t, 1H), 7.66 (d, 1H), 7.70 (d, 1H); EI-MS 341.0 (M+1).

Example 244 4-Chloro-8-methoxy-2-(2-trifluoromethyl-phenyl)-quinazoline (B19): Prepared from 8-methoxy-2-(2-trifluoromethyl-phenyl)-3H-quinazolin-4-one (1.0g, 3.12mmol), triethylamine hydrochloride (472mg, 3.43mmol), and POCl₃. Purification by flash chromatography afforded a white solid (89% yield). HPLC-Method A, R_t 4.10 min, (98%), MS (m/z) 258.08 (M+H).

Example 245 2-(4-Chloro-quinazolin-2-yl)-benzonitrile (B20): Prepared to afford a yellow solid in 1.5% yield. $^1\text{H-NMR}$ (500 MHz, CDCl₃) δ 8.47 (d, 1H), 8.24 (d, 1H), 8.16 (d, 1H), 8.07 (impurity), 7.94 (t, 1H), 7.92 (impurity),

7.86 (d, 1H), 7.68 (m, 2H), 7.65 (impurity), 7.54 (impurity), 7.49 (t, 1H), 4.2 (impurity), 1.05 (impurity) ppm; MS (LC/MS) 266.05 (M+H); HPLC-Method A, R_t 3.88 min.

5 Example 246 6-Methyl-2-(2-trifluoromethyl-phenyl)-3H-pyrimidin-4-one (D3): Prepared to afford a yellow solid in 50% yield. ¹H-NMR (500 MHz, DMSO-d6) δ 12.7 (br s, 1H), 7.9 (m, 1H), 7.8 (m, 2H), 7.7 (m, 1H), 6.3 (s, 1H), 2.21 (s, 3H) ppm; MS (FIA) 255.0 (M+H); HPLC-Method A, R_t 10 2.578 min.

15 Example 247 6-Cyclohexyl-2-(2-trifluoromethyl-phenyl)-3H-pyrimidin-4-one (D4): Prepared to afford an off-white solid in 54% yield. ¹H-NMR (500 MHz, DMSO-d6) δ 12.9 (br s, 1H), 7.9 (m, 4H), 6.3 (s, 1H), 2.5 (m, 1H), 1.9 (m, 5H), 1.4 (m, 5H) ppm; MS (FIA) 323.1 (M+H); HPLC-Method A, R_t 3.842 min.

20 Example 248 2-(2-Chloro-5-trifluoromethyl-phenyl)-3H-quinazoli-4-one (D10): ¹HNMR (500MHz, CD₃OD) δ 8.32-8.25 (m, 1H), 8.01 (s, 1H), 7.91-7.72 (m, 1H), 7.66-7.55 (m, 1H). LC-MS (ES+) 325.01 (M+H). HPLC-Method D, R_t 3.29 min.

25 Example 249 2-(4-Fluoro-2-trifluoromethyl-phenyl)-3H-quinazolin-4-one (D14): ¹HNMR (500MHz, CD₃OD) δ 8.28 (d, 8.0Hz, 1H), 7.94-7.84 (m, 1H), 7.84-7.77 (m, 1H), 7.76-7.67 (m, 2H), 7.65-7.53 (m, 2H). LC-MS (ES+) 309.06 (M+H). HPLC-Method D, R_t 2.88 min.

30

Example 250 2-(4-Nitro-2-chloro-phenyl)-3H-quinazolin-4-one (D15): LC-MS (ES+) 302.03 (M+H). HPLC-Method D, R_t 2.81 min.

Example 251 2-(5-Fluoro-2-trifluoromethyl-phenyl)-3*H*-quinazolin-4-one (D17): ^1H NMR (500MHz, CD₃OD) δ 8.28 (d, R_t J=8.05Hz, 1H), 7.96 (dd, J=5.05, 8.55Hz, 1H), 7.89 (t, J=7.9Hz, 1H), 7.78-7.69 (m, 1H), 7.66-7.46 (m, 3H). LC-MS (ES+) 309.14 (M+H). HPLC-Method D, R_t 2.90 min.

Example 252 (1*H*-Indazol-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (III-1): Prepared by Method A in DMF to afford 70. 10 mg (50% yield) as pale yellow solid. ^1H NMR (500 MHz, DMSO-d₆) δ 13.1 (s, br, 1H), 8.48 (d, 1H), 7.91 (d, 2H), 7.76 (br, 2H), 7.45 (m, 2H), 7.36 (d, 1H), 7.20 (m, 4H), 6.86 (t, 1H) ppm. MS (ES+) 338.07 (M+H); (ES-) 336.11 (M- H); HPLC-Method A, R_t 2.88 min.

Example 253 (5-Methyl-2*H*-pyrazol-3-yl)-(2-phenyl-5,6,7,8-tetrahydroquinazolin-4-yl)-amine (III-7): Prepared according to Method A. ^1H NMR (500 MHz, DMSO-d₆) δ 12.1 (s, br, 1H), 8.70 (s, br, 1H), 8.37 (d, J = 6.7 Hz, 2H), 20 7.54 (m, 3H), 6.67 (s, 1H), 2.82 (m, 2H), 2.68 (m, 2H), 2.37 (s, 3H), 1.90 (s, br, 4H); MS 306.1 (M+H).

Example 254 (5-Methyl-2*H*-pyrazol-3-yl)-(2-phenyl-6,7,8,9-tetrahydro-5*H*-cycloheptapyrimidin-4-yl)-amine (III-8): MS 25 320.48 (M+H); HPLC-Method E, R_t 1.124 min.

Example 255 (5-Methyl-2*H*-pyrazol-3-yl)-(2-pyridin-4-yl-quinazolin-4-yl)-amine (III-9): Yellow solid, mp 286-289°C, ^1H NMR (DMSO) δ 2.35 (3H, s), 6.76 (1H, s), 7.61 (1H, m), 7.89 (2H, m), 8.32 (2H, d), 8.70 (1H, d), 8.78 (2H, d), 10.56 (1H, br s), 12.30 (1H, br s); IR (solid) 1620, 1598, 1571, 1554, 1483, 1413, 1370, 1328; MS 303.2 (M+H)⁺

Example 256 (7-Chloro-2-pyridin-4-yl-quinazolin-4-yl)-(5-methyl-2H-pyrazol-3-yl)-amine (III-28): ^1H NMR (DMSO-d₆) δ 2.35 (3H, s), 6.75 (1H, s), 7.65 (1H, d), 7.93 (1H, s), 8.30 (2H, d), 8.73 (1H, d), 8.79 (2H, d), 10.69 (1H, s), 12.33 (1H, s); MS m/z 337.2 (M+H)⁺.

Example 257 (6-Chloro-2-pyridin-4-yl-quinazolin-4-yl)-(5-methyl-2H-pyrazol-3-yl)-amine (III-29): ^1H NMR (DMSO-d₆) δ 2.31 (3H, s), 6.74 (1H, s), 7.89 (1H, s), 8.30 (2H, d), 8.80 (2H, d), 8.91 (1H, s), 10.63 (1H, s), 12.29 (1H, s); MS 337.2 (M+H)⁺.

Example 258 (2-Cyclohexyl-quinazolin-4-yl)-(5-methyl-2H-pyrazol-3-yl)-amine (III-30): ^1H NMR (DMSO) δ 2.35 (3H, s), 1.70 (3H, m), 1.87 (2H, d), 1.99 (2H, d), 2.95 (1H, t), 6.72 (1H, s), 7.75 (1H, d), 7.88 (1H, s), 7.96 (1H, s), 8.83 (1H, s), 11.95 (1H, s), 12.70 (1H, s); MS 308.4 (M+H)⁺.

Example 259 (5-Methyl-2H-pyrazol-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (III-31): mp 246°C; ^1H NMR (400MHz) δ 2.35 (3H, s), 6.70 (1H, br s), 7.51-7.57 (4H, m), 7.83-7.84 (2H, d), 8.47-8.50 (2H, d), 8.65 (1H, d), 10.4 (1H, s), 12.2 (1H, bs); IR (solid) 3696, 3680, 2972, 2922, 2865; MS 302.1 (M+H)⁺.

Example 260 [2-(4-Iodophenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-32): ^1H NMR (DMSO-d₆) δ 2.34 (3H, s), 6.72 (1H, s), 7.56 (1H, d), 7.84 (2H, d), 7.93 (2H, d), 8.23 (2H, d), 8.65 (1H, s), 10.44 (1H, s), 12.24 (1H, s); MS 428.5 (M+H)⁺.

Example 261 [2-(3,4-Dichlorophenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-33): A suspension of 2-(3,4-dichloro-phenyl)-3H-quinazolin-4-one (1g, 3.43 mmol) in phosphorus oxychloride (4 mL) was stirred at 5 110°C for 3 hours. The solvent was removed by evaporation and the residue is treated carefully with cold aqueous, saturated NaHCO₃. The resulting solid was collected by filtration and washed with ether to afford 4-chloro-2-(3,5-dichloro-phenyl)-quinazoline as a white solid (993 mg, 93%). To the above compound (400mg, 1.29 mmol) in THF (30 mL) was added 3-amino-5-methyl pyrazole (396 mg, 2.58 mmol) and the resulting mixture heated at 65°C overnight. The solvents were evaporated and the residue triturated with ethyl acetate, filtered, and washed with 10 the minimum amount of ethanol to afford compound III-33 as a white solid (311 mg 65%): mp 274°C; ¹H NMR (DMSO) δ 2.34 (3H, s), 6.69 (1H, s), 7.60 (1H, m), 7.84 (1H, d), 7.96 (2H, d), 8.39 (1H, dd), 8.60 (1H, d), 8.65 (1H, d), 10.51 (1H, s), 12.30 (1H, s); IR (solid) 1619, 1600, 15 1559, 1528, 1476, 1449, 1376, 1352, 797, 764, 738; MS 1559, 1528, 1476, 1449, 1376, 1352, 797, 764, 738; MS 370.5 (M+H)⁺.

Example 262 [2-(4-Bromophenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-34): mp 262-265°C; ¹H NMR (DMSO) δ 2.34 (3S, s), 6.73 (1H, s), 7.55 (1H, m), 25 7.74 (2H, d), 7.83 (2H, m), 8.40 (2H, d), 8.65 (1H, d), 10.44 (1H, s), 12.25 (1H, s); IR (solid) 1603, 1579, 1546, 1484, 1408, 1365; MS 380.1/382.1 (M+H)⁺.

30 Example 263 [2-(4-Chlorophenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-35): mp >300°C; ¹H NMR (DMSO) δ 2.34 (3H, s), 6.74 (1H, s), 7.53-7.62 (3H, m), 7.84 (2H, d), 8.47 (2H, d), 8.65 (1H, d), 10.44 (1H, s),

12.26 (1H, s); IR (solid) 1628, 1608, 1584, 1546, 1489,
1408, 1369, 1169; MS 336.2 (M+H)+.

Example 264 [2-(3,5-Dichlorophenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-36): mp 228°C; ¹H NMR (DMSO) δ 2.34 (3H, s), 6.69 (1H, s), 7.96 (1H, d), 8.21 (3H, m), 8.56 (1H, d), 8.60 (2H, d), 10.51 (1H, s), 12.30 (1H, s); IR (solid) 1546, 1331, 802, 763, 729, 658, 652; MS 370.5 (M+H)+.

10

Example 265 [2-(4-Cyanophenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-37): mp 263°C; ¹H NMR (DMSO) δ 2.34 (3H, s), 6.72 (1H, s), 7.61 (1H, d), 7.88 (2H, s), 8.04 (2H, d), 8.63 (2H, d), 8.67 (1H, s), 10.52 (1H, s), 12.27 (1H, s); IR (solid) 1739, 1436, 1366, 1229, 1217; MS 327.2 (M+H)+.

Example 266 [2-(3-Iodophenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-38): mp 234-235°C; ¹H NMR (DMSO) δ 2.35 (3H, s), 6.73 (1H, s), 7.35 (1H, m), 7.56 (1H, m), 7.85 (3H, m), 8.47 (1H, m), 8.65 (1H, m), 8.86 (1H, s), 10.49 (1H, s), 12.28 (1H, br s); IR (solid) 1560, 1541, 1469, 1360; MS 428.1 (M+H)+.

Example 267 [2-(4-Ethylsulfanylphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-39): mp 229-231°C; ¹H NMR (DMSO) δ 1.29 (3H, t), 2.35 (3H, s), 3.07 (2H, q), 6.76 (1H, s), 7.43 (2H, d), 7.51 (1H, m), 7.81 (2H, m), 8.41 (2H, d), 8.64 (1H, d), 10.38 (1H, s), 12.24 (1H, br s); IR (solid) 1587, 1574, 1555, 1531, 1484, 1412, 1369; MS 362.1 (M+H)+.

Example 268 (5-Cyclopropyl-2H-pyrazol-3-yl)- (2-phenyl-quinazolin-4-yl)-amine (III-40): mp 218-219°C; ¹H NMR (DMSO-d₆) δ 0.70-0.80 (2H, m), 0.90-1.00 (2H, m), 6.70 (1H, s), 7.45-7.55 (4H, m), 7.80-7.85 (2H, m), 8.45-8.55 (2H, m), 8.65 (1H, d), 10.40 (1H, s), 12.27 (1H, s); IR (solid) 1624, 1605, 1591, 1572, 1561, 1533, 1479, 1439, 1419, 1361, 1327, 997, 828, 803, 780, 762, 710; MS 328.2 (M+H)⁺.

10 Example 269 [2-(4-tert-Butylphenyl)-quinazolin-4-yl]- (5-methyl-2H-pyrazol-3-yl)-amine (III-41): mp >300°C; ¹H NMR (DMSO-d₆) δ 1.35 (9H, s), 2.34 (3H, s), 6.79 (1H, s), 7.55 (3H, d), 7.85 (2H, d), 8.39 (2H, d), 8.62 (1H, d), 10.35 (1H, s), 12.22 (1H, s); IR (solid) 1603, 1599, 1577, 1561, 1535, 1481, 1409, 1371, 1359, 998, 841, 825, 766, 757; MS 358.3 (M+H)⁺.

20 Example 270 [2-(4-Chlorophenyl)-quinazolin-4-yl]- (5-cyclopropyl-2H-pyrazol-3-yl)-amine (III-42): ¹H NMR (DMSO-d₆) δ 0.77 (4H, br m), 2.05 (1H, m), 6.59 (1H, s), 7.60 (1H, d), 7.85 (2H, d), 7.91 (2H, d), 8.22 (2H, d), 8.65 (1H, s), 10.51 (1H, s), 12.33 (1H, s); MS 362.1 (M+H)⁺.

25 Example 271 (2-Benzo[1,3]dioxol-5-yl-quinazolin-4-yl)- (5-methyl-2H-pyrazol-3-yl)-amine (III-43): ¹H NMR (DMSO) δ 2.33 (3H, s), 6.13 (2H, s), 6.78 (1H, s), 7.11 (1H, d), 7.80 (1H, t), 7.94 (1H, s), 8.09 (3H, m), 8.25 (1H, d), 10.34 (1H, s), 12.21 (1H, s); MS 346.5 (M+H)⁺.

30 Example 272 [2-(4-Dimethylaminophenyl)-quinazolin-4-yl]- (5-methyl-2H-pyrazol-3-yl)-amine (III-44): ¹H NMR (DMSO-d₆) δ 2.02 (6H, s), 2.39 (3H, s), 6.83 (1H, s), 7.71 (1H,

d), 7.98 (2H, s), 8.04 (2H, d), 8.33 (2H, d), 8.67 (1H, s), 11.82 (1H, s), 12.72 (1H, s); MS 345.3 (M+H)⁺.

Example 273 [2-(3-Methoxyphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-45): mp 226°C; ¹H NMR (DMSO) δ 2.34 (3H, s), 3.92 (3H, s), 6.72 (1H, s), 7.21 (1H, d), 7.57 (1H, t), 7.79 (1H, t), 8.02 (3H, m), 8.14 (1H, s), 8.79 (1H, d), 10.39 (1H, s), 12.22 (1H, s); IR (solid) 1599, 1572, 1538, 1478, 1427, 1359, 833, 761, 661; MS 332.2 (M+H)⁺.

Example 275 (5-Cyclopropyl-2H-pyrazol-3-yl)-[2-(3,4-dichlorophenyl)-quinazolin-4-yl]-amine (III-46): ¹H NMR (DMSO-d6) δ 0.86 (2H, d), 1.02 (2H, d), 1.69 (1H, m), 6.56 (1H, s), 7.57 (1H, d), 7.84 (4H, m), 8.40 (1H, d), 8.58 (1H, s), 8.64 (1H, s), 10.53 (1H, s), 12.36 (1H, s); MS 396.0 (M+H)⁺.

Example 276 (2-Biphenyl-4-yl-quinazolin-4-yl)-(5-methyl-2H-pyrazol-3-yl)-amine (III-47): To a mixture of [2-(4-bromo-phenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-34) (196 mg, 0.51 mmol) and phenylboronic acid (75 mg, 0.62 mmol) in THF:water (1:1, 4 mL) was added Na₂CO₃ (219 mg, 2.06 mmol), triphenylphosphine (9mg, 1/15 mol%) and palladium acetate (1 mg, 1:135 mol%). The resulting mixture was heated at 80°C overnight, the solvents were evaporated and the residue purified by flash chromatography (gradient of dichloromethane:MeOH) to afford III-21 as a yellow solid (99 mg, 51%): ¹H NMR (DMSO) δ 2.37 (3H, s), 6.82 (1H, s), 7.39-7.57 (4H, m), 7.73-7.87 (6H, m), 8.57 (2H, d), 8.67 (1H, d), 10.42 (1H, s), 12.27 (1H, s); MS 378.2 (M+H)⁺.

Example 277 [2-(4-Ethynylphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-48): To a mixture of [2-(4-bromo-phenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-34) (114 mg, 0.3 mmol), and trimethylsilylacetylene (147 mg, 1.5 mmol) in DMF (2 mL) was added CuI (1.1 mg, 1:50 mol%), Pd(PPh₃)₂Cl₂ (4.2 mg, 1:50 mol%) and triethylamine (121 mg, 0.36 mmol). The resulting mixture was heated at 120°C overnight and the solvent evaporated. The residue was triturated in ethyl acetate and the resulting precipitate collected by filtration. The collected solid was suspended in THF (3 mL) and TBAF (1M in THF, 1.1eq) was added. The reaction mixture was stirred at room temperature for 2 hours and the solvent evaporated. The residue was purified by flash chromatography (silica gel, gradient of DCM:MeOH) to afford III-48 as a white solid (68 mg, 70%): ¹H NMR (DMSO) δ 2.34 (3H, s), 4.36 (1H, s), 6.74 (1H, s), 7.55 (1H, m), 7.65 (2H, d), 7.84 (2H, m), 8.47 (2H, d), 8.65 (1H, d), 10.43 (1H, s), 12.24 (1H, s); MS 326.1 (M+H)⁺.

20

Example 278 [2-(3-Ethynylphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-49): mp 204-207°C; ¹H NMR (DMSO) δ 2.34 (3H, s), 4.28 (1H, s), 6.74 (1H, s), 7.55-7.63 (3H, m), 7.83-7.87 (2H, m), 8.49 (1H, d), 8.57 (1H, s), 8.65 (1H, d), 10.46 (1H, s), 12.27 (1H, s); IR (solid) 1598, 1574, 1541, 1489, 1474, 1422, 1365; MS 326.1 (M+H)⁺.

30 Example 279 [2-(3-Methylphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-50): A suspension of 1*H*-quinazoline-2,4-dione (10.0 g, 61.7 mmol) in POCl₃ (60 mL, 644 mmol) and N,N-dimethylaniline (8mL, 63.1 mmol) was heated under reflux for 2 h. The excess POCl₃ was

removed in vacuo, the residue poured into ice, and the resulting precipitate collected by filtration. The crude solid product 2,4-dichloro-quinazoline (6.5 g, 53% yield) was washed with water and dried under vacuum for next 5 step use without further purification. To a solution of the 2,4-dichloro-quinazoline (3.3 g, 16.6 mmol) in anhydrous ethanol (150 mL) was added 5-methyl-1*H*-pyrazol-3-yl amine (3.2 g, 32.9 mmol) and the resulting mixture was stirred at room temperature for 4 hours. The 10 resulting precipitate was collected by filtration, washed with ethanol, and dried under vacuum to afford 4.0 g (93% yield) of (2-chloro-quinazolin-4-yl)-(5-methyl-1*H*-pyrazol-3-yl)-amine which was used in the next step without further purification. To a solution of the (2-chloro-quinazolin-4-yl)-(5-methyl-1*H*-pyrazol-3-yl)-amine 15 (50 mg, 0.19 mmol) in DMF (1.0 mL) was added *m*-tolyl boronic acid (0.38 mmol), 2M Na₂CO₃ (0.96 mmol), and tri-*t*-butylphosphine (0.19 mmol). The flask was flushed with nitrogen and the catalyst PdCl₂(dppf) (0.011 mmol) added 20 in one portion. The reaction mixture was then heated at 80°C for 10 hours, cooled to room temperature, and poured into water (2 mL). The resulting precipitate was collected by filtration, washed with water, and purified by HPLC to afford III-50 as a pale yellow solid (61mg, 25 75%): ¹H NMR (500 MHz, DMSO-d6) δ 12.3 (br s, 1H), 10.4 (br s, 1H), 8.75 (d, 1H), 8.30 (s, 1H), 8.25 (d, 1H), 7.78 (s, 2H), 7.55 (m, 1H), 7.45 (m, 1H), 7.35 (m, 1H), 6.80 (s, 1H), 2.47 (s, 3H), 2.30 (s, 3H); MS 316.1 (M+H).

30 Example 280 [2-(3,5-Difluorophenyl)-quinazolin-4-yl]-(5-methyl-2*H*-pyrazol-3-yl)-amine (III-51): ¹H NMR (500 MHz, DMSO-d6) δ 12.3 (br s, 1H), 10.8 (br s, 1H), 8.63 (d, 1H),

7.95 (d, 2H), 7.85 (m, 2H), 7.58 (t, 1H), 7.41 (t, 1H),
6.59 (s, 1H), 2.27 (s, 3H); MS 338.1 (M+H).

Example 281 [2-(3-Chloro-4-fluorophenyl)-quinazolin-4-yl]-
5 (5-methyl-2H-pyrazol-3-yl)-amine (III-52): ¹H NMR (500
MHz, DMSO-d6) δ 12.4 (br s, 1H), 10.8 (br s, 1H), 8.65 (d,
1H), 8.50 (d, 1H), 8.36 (m, 1H), 7.85 (m, 1H), 7.60 (m,
1H), 6.62 (s, 1H), 2.30 (s, 3H); MS 354.1 (M+H).

Example 282 (5-Methyl-2H-pyrazol-3-yl)-[2-(3-trifluoromethylphenyl)-quinazolin-4-yl]-amine (III-53): ¹H
NMR (500 MHz, DMSO-d6) δ 12.2 (br, 1H), 10.45 (br, 1H),
7.53 (s, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.06 (d, J = 8.2
Hz, 1H), 6.65 (d, J = 8.3 Hz, 1H), 6.57 (t, J = 7.6 Hz,
1H), 6.51 (d, J = 7.8 Hz, 1H), 6.43 (t, J = 7.8 Hz, 1H),
6.32 (t, J = 7.6 Hz, 1H), 5.51 (s, 1H), 2.03 (s, 3H); MS
370.2 (M+H).

Example 283 [2-(3-Cyanophenyl)-quinazolin-4-yl]-
20 (5-methyl-2H-pyrazol-3-yl)-amine (III-54): ¹H NMR (500 MHz,
DMSO-d6) δ 9.01 (s, 1H), 8.96 (m, 2H), 8.28 (d, J = 7.3
Hz, 1H), 8.16 (s, br, 2H), 8.06 (t, J = 7.8 Hz, 1H), 7.88
(m, 1H), 6.96 (s, 1H), 2.58 (s, 3H); MS 327.1 (M+H).

Example 284 [2-(3-Isopropylphenyl)-quinazolin-4-yl]-
25 (5-methyl-2H-pyrazol-3-yl)-amine (III-55): ¹H NMR (500 MHz,
DMSO-d6) δ 8.89 (d, J = 7.5 Hz, 1H), 8.37 (s, 1H), 8.26
(s, 1H), 8.08 (m, 2H), 7.81 (t, br, 1H), 7.67 (m, 2H),
6.88 (s, 1H), 3.12 (m, 1H), 2.40 (s, 3H), 1.38 (d, J =
30 6.9 Hz, 6H); MS 344.2 (M+H).

Example 285 (5-Methyl-2H-pyrazol-3-yl)-(2-pyridin-3-yl-
quinazolin-4-yl)-amine (III-56): ¹H NMR (500 MHz, DMSO-d6)

δ 9.50 (s, 1H), 8.84 (d, J = 7.3 Hz, 1H), 8.80 (d, J = 4.4 Hz, 1H), 8.66 (d, J = 8.2 Hz, 1H), 7.87 (m, 2H), 7.77 (m, 1H), 7.60 (t, J = 7.2 Hz, 1H), 6.67 (s, 1H), 2.28 (s, 3H); MS 303.1 (M+H).

5

Example 286 [2-(3-Acetylphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-57): ¹H NMR (500 MHz, DMSO-d6) δ 8.80 (s, 1H), 8.55 (d, J = 7.7 Hz, 1H), 8.42 (d, J = 7.6 Hz, 1H), 8.00 (d, J = 7.0 Hz, 1H), 7.76 (m, 2H), 7.58 (t, J = 7.7 Hz, 1H), 7.48 (s, br, 1H), 6.60 (s, 1H), 2.49 (s, 3H), 2.03 (s, 3H); MS 344.1 (M+H).

Example 287 [2-(3,5-Ditrifluoromethylphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-58): ¹H NMR (500 MHz, DMSO-d6) δ 10.7 (s, br, 1H), 8.95 (s, 2H), 8.63 (d, J = 8.2 Hz, 1H), 8.25 (s, 1H), 7.86 (m, 2H), 7.58 (t, J = 6.9 Hz, 1H), 6.62 (s, 1H), 2.26 (s, 3H); MS 438.1 (M+H).

Example 288 [2-(3-Hydroxymethylphenyl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-59): ¹H NMR (500 MHz, DMSO-d6) δ 8.74 (d, J = 7.9 Hz, 1H), 8.33 (s, 1H), 8.17 (s, br, 1H), 7.95 (s, br, 1H), 7.89 (s, br, 1H), 7.62 (m, 3H), 6.72 (s, 1H), 5.53 (s, 1H), 4.60 (s, 2H), 2.28 (s, 3H); MS 332.1 (M+H).

Example 289 (5-Methyl-2H-pyrazol-3-yl)-[2-(3-phenoxyphenyl)-quinazolin-4-yl]-amine (III-60): mp 231-232°C; ¹H NMR (DMSO-d6) δ 2.21 (3H, s), 6.59 (1H, s), 7.10-7.22 (4H, m), 7.41-7.45 (2H, m), 7.54-7.59 (2H, m), 7.81 (2H, s), 8.09 (1H, s), 8.27 (1H, m), 8.64 (1H, m), 10.40 (1H, s), 12.20 (1H, s); IR (solid); IR (solid) 1589, 1560, 1541, 1536, 1484, 1360, 1227; MS 394.7 (M+H)⁺.

Example 290 (5-Cyclopropyl-2H-pyrazol-3-yl)-[2-(3-phenoxyphenyl)-quinazolin-4-yl]-amine (III-61): mp 193-195°C; ¹H NMR (DMSO-d₆) δ 0.67 (2H, m), 0.93 (2H, m), 1.87 (1H, m), 6.56 (1H, s), 7.06-7.20 (4H, m), 7.40-7.43 (2H, m), 7.55-7.59 (2H, m), 7.81 (2H, s), 8.11 (1H, s), 8.27 (1H, m), 8.63 (1H, m), 10.43 (1H, s), 12.26 (1H, s); IR (solid); IR (solid) 1589, 1574, 1527, 1483, 1369, 1226; MS 420.7 (M+H)⁺.

10

Example 291 (5-Methyl-2H-pyrazol-3-yl)-(2-thiophen-3-yl-quinazolin-4-yl)-amine (III-62): ¹H NMR (500 MHz, DMSO-d₆) δ 11.78 (s, br, 1H), 8.75 (d, J = 8.1 Hz, 1H), 8.68 (s, 1H), 7.98 (dd, J = 7.9, 7.5 Hz, 1H), 7.89 (m, 2H), 7.81 (m, 1H), 7.68 (t, J = 7.5 Hz, 1H), 6.69 (s, 1H), 2.30 (s, 3H); MS 308.1 (M+H).

Example 292 (2-Phenyl-quinazolin-4-yl)-(2H-pyrazol-3-yl)-amine (III-63): mp 247-249°C; ¹H NMR (DMSO) δ 6.99 (1H, br s), 7.49-7.58 (5H, m), 7.81 (1H, br s), 7.83 (2H, m), 8.47-8.49 (2H, m), 8.66 (1H, d), 10.54 (1H, s), 12.59 (1H, s); IR (solid) 3145, 2922, 1622, 1597; MS 288.2 (M+H)⁺.

25 Example 293 (2H-Pyrazol-3-yl)-(2-pyridin-4-yl-quinazolin-4-yl)-amine (III-64): mp 285-286°C; ¹H NMR (DMSO) δ 6.99 (1H, br s), 7.65 (1H, m), 7.81-7.94 (3H, m), 8.3-8.35 (2H, m), 8.73 (1H, d), 8.84-8.90 (2H, m), 10.76 (1H, s), 12.6 (1H, s); IR (solid) 3180, 2972, 1600, 1574; MS 289.2 (M+H)⁺.

30 Example 294 5-Ethyl-2H-pyrazol-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (III-65): mp 221-222°C; ¹H NMR

(DMSO) δ 1.31 (3H, t), 2.68 (2H, d), 6.80 (1H, s), 7.50-7.60 (4H, m), 8.45-8.55 (2H, m), 8.65-8.75 (1H, m), 10.44 (1H, s), 12.27 (1H, s); IR (solid) 3190, 1622, 1595, 1575, 1533, 1482, 1441, 1420, 1403, 1361, 758, 711; MS 316.2
5 (M+H)⁺.

Example 295 (2-Phenyl-quinazolin-4-yl)- (5-propyl-2H-pyrazol-3-yl)-amine (III-66): mp 204-205°C; ¹H NMR (DMSO-d6) δ 1.02 (3H, t), 1.66-1.75 (2H, m), 2.69 (2H, t), 6.80 (1H, s), 7.45-7.60 (4H, m), 7.80-7.88 (2H, m), 8.45-8.50 (2H, m), 8.65 (1H, d), 10.39 (1H, s), 12.25 (1H, s); IR (solid) 1621, 1560, 1572, 1533, 1479, 1441, 1421, 1363, 1328, 999, 827, 808, 763, 709, 697; MS 330.2 (M+H)⁺.

15 Example 296 (5-Isopropyl-2H-pyrazol-3-yl)- (2-phenyl-quinazolin-4-yl)-amine (III-67): mp 218-219°C; ¹H NMR (DMSO-d6) δ 1.36 (6H, d), 3.05 (1H, m), 6.86 (1H, s), 7.48-7.59 (4H, m), 7.80-7.88 (2H, m), 8.49-8.58 (2H, m), 8.66 (1H, d), 10.47 (1H, s), 12.30 (1H, s); IR (solid) 3173, 2968, 1619, 1593, 1573, 1533, 1478, 1438, 1413, 1398, 1363, 1329, 995, 822, 798, 761, 707, 666, 659; MS 330.2 (M+H)⁺.

25 Example 297 (5-tert-Butyl-2H-pyrazol-3-yl)- (2-phenyl-quinazolin-4-yl)-amine (III-68): mp 136-137°C; ¹H NMR (DMSO-d6) δ 1.38 (9H, s), 6.87 (1H, br s), 7.51-7.57 (4H, m), 7.84-7.85 (2H, m), 8.49-8.51 (2H, m), 8.65 (1H, d), 10.43 (1H, s), 12.21 (1H, br s); IR (solid) 3162, 2963, 1621, 1590, 1572; MS 344.2 (M+H)⁺.

30 Example 298 (5-tert-Butyl-2H-pyrazol-3-yl)- (2-pyridin-4-yl-quinazolin-4-yl)-amine (III-69): mp >300°C; ¹H NMR (DMSO) δ 1.38 (9H, s), 6.82 (1H, br s), 7.63 (1H, m),

7.86-7.91 (2H, m), 8.32-8.33 (2H, d), 8.69 (1H, d),
8.75-8.76 (2H, d), 10.60 (1H, s), 12.31 (1H, br s); IR
(solid) 3683, 3149, 2963, 1621; MS 345.2(M+H)⁺.

5 Example 299 (5-Cyclopentyl-2*H*-pyrazol-3-yl)- (2-phenyl-
quinazolin-4-yl)-amine (III-70): mp 240-241°C; ¹H NMR
(DMSO-d6) δ 1.68-1.89 (6H, m), 2.03-2.17 (2H, m), 3.14-
3.22 (1H, m), 6.80 (1H, s), 7.50-7.60 (4H, m), 7.80-7.89
(2H, m), 8.45-8.52 (2H, m), 8.67 (1H, d), 10.52 (1H, s),
10 12.26 (1H, s); IR (solid) 2957, 1621, 1591, 1571, 1531,
1476, 1438, 1405, 1370, 1325, 999, 951, 801, 775, 761,
747, 710695, 668, 654; MS 356.2(M+H)+.

15 Example 300 (5-Phenyl-2*H*-pyrazol-3-yl)- (2-phenyl-
quinazolin-4-yl)-amine (III-71): mp 207-209°C; ¹H NMR
(DMSO) δ 7.38-7.40 (1H, m), 7.50-7.58 (6H, m), 7.82-7.88
(4H, m), 8.51 (2H, m), 8.67 (1H, s), 10.58 (1H, s), 13.11
(1H, br s); IR (solid) 3345, 3108, 1627, 1612; MS 364.2
(M+H)⁺.

20 Example 301 (5-Carboxy-2*H*-pyrazol-3-yl)- (2-phenyl-
quinazolin-4-yl)-amine (III-72): (5-Methoxycarbonyl-2*H*-
pyrazol-3-yl)- (2-phenyl-quinazolin-4-yl)-amine (III-73)
(345mg, 1 mmole in THF, 6 mL) was treated with NaOH (1M,
25 4.0 mL), stirred at 50°C for 5 hours, cooled to room
temperature, and neutralised with 1M HCl. The mixture
was concentrated *in vacuo* to remove THF then diluted with
water and the resulting precipitate filtered. The
residual solid was dried at 80°C under vacuum to afford
30 III-72 as an off-white solid (312 mg, 94%): mp 289-291°C
(dec.); ¹H NMR (DMSO) δ 7.45 (1H, br s), 7.50-7.60 (5H,
m), 7.80-7.88 (2H, m), 7.40-7.50 (2H, m), 8.60-8.70 (1H,
d), 10.70 (1H, s), 13.00-13.80 (2H, br s); IR (solid)

1699, 1624, 1607, 1570, 1539, 1506, 1486, 1398, 1333,
1256, 1177, 1004, 827, 764, 705; MS 332.3 (M+H)⁺.

Example 302 (**5-Methoxycarbonyl-2H-pyrazol-3-yl**) - (2-phenyl-quinazolin-4-yl)-amine (**III-73**): mp 271-273°C; ¹H NMR (DMSO) δ 3.95 (3H, s), 7.50-7.65 (5H, m), 7.80-7.98 (2H, m), 8.40-8.50 (2H, m), 8.65-8.73 (1H, m), 10.80 (1H, s), 13.80 (1H, s); IR (solid) 3359, 1720, 1624, 1597, 1561, 1538, 1500, 1475, 1435, 1410, 1358, 1329, 1283, 1261, 1146, 1125, 1018, 1010, 944, 827, 806, 780, 763, 703, 690, 670; MS 346.3 (M+H)⁺.

Example 303 (**5-Hydroxymethyl-2H-pyrazol-3-yl**) - (2-phenyl-quinazolin-4-yl)-amine (**III-74**): A solution of (**5-Methoxycarbonyl-2H-pyrazol-3-yl**) - (2-phenyl-quinazolin-4-yl)-amine (**III-73**) (345mg, 1mmol) in anhydrous THF (10mL) was treated with lithium borohydride (125mg, 5.75 mmol) at 65°C for 5 hours. The mixture was cooled to room temperature then combined with 2M HCl and ethyl acetate. Solid sodium hydrogen carbonate was added to achieve pH 8 and the resulting mixture extracted with ethyl acetate. The extracts were dried over magnesium sulphate and concentrated. Purification by flash chromatography (SiO₂, methanol-dichloromethane gradient) afforded **III-74** (95 mg, 30%) as an off-white solid: mp 238-239°C; ¹H NMR (DMSO) δ 4.58 (2H, d, CH₂), 5.35 (1H, s, OH), 6.94 (1H, s), 7.50-7.60 (4H, m), 7.85-7.90 (2H, m), 8.48-8.54 (2H, m), 8.69 (1H, 1H), 10.40 (1H, s), 12.48 (1H, s); IR (solid) 1652, 1621, 1603, 1575, 1558, 1539, 1532, 1480, 1373, 1320, 1276, 1175, 1057, 1037, 1007, 951, 865, 843, 793, 780, 7124; MS 318.2 (M+H)⁺.

Example 304 (5-Methoxymethyl-2H-pyrazol-3-yl)- (2-phenyl-quinazolin-4-yl)-amine (III-75): mp 190-191°C; ¹H NMR (DMSO) δ 3.34 (3H, s), 4.45 (2H, s), 7.00 (1H, s), 7.50-7.62 (4H, m), 7.82-7.90 (2H, m), 8.45-8.52 (2H, m), 8.65 (1H, br s), 10.50 (1H, s), 12.30 (1H, s); IR (solid) 3177, 1606, 1589, 1530, 1479, 1441, 1406, 1374, 1363, 1329, 1152, 1099, 999, 954, 834, 813, 766, 707, 691; MS 332.3 (M+H)⁺.

10 Example 305 [5-(3-Hydroxyprop-1-yl)-2H-pyrazol-3-yl]- (2-phenyl-quinazolin-4-yl)-amine (III-76): A solution of (5-benzyloxypropyl-2H-pyrazol-3-yl)- (2-phenyl-quinazolin-4-yl)-amine (III-78) (200mg, 0.46mmol) in toluene (4mL) and acetonitrile (8mL) was stirred with trimethylsilyl iodide (0.64ml, 4.6mmol) at 55°C for 3 hours to afford an amber coloured solution. This mixture was diluted with ethyl acetate and aqueous sodium hydrogen carbonate. The resulting layers were separated, the organic layer was dried over magnesium sulphate and concentrated *in vacuo*.

15 Purification by flash chromatography (SiO₂, methanol-dichloromethane gradient) affords a yellow oil (115mg). Trituration with dichloromethane affords III-76 as an off-white solid dried at 75°C under vacuum (83mg, 52%): mp 164-165°C; ¹H NMR (DMSO) δ 1.80-1.90 (2H, m), 2.70-2.80 (2H, m), 3.50-3.60 (2H, m), 4.59 (1H, s), 6.80 (1H, s), 7.50-7.60 (4H, m), 7.82-7.90 (2H, m), 8.48-8.53 (2H, m), 8.63 (1H, s), 10.40 (1H, s), 12.25 (1H, s); IR (solid) 1622, 1587, 1574, 1562, 1528, 1480, 1440, 1421, 1368, 1329, 1173, 1052, 1030, 1006, 952, 833, 762, 734, 706,

20 25 30 690, 671, 665; MS 346.0 (M+H)⁺.

Example 306 [5-(3-Methoxyprop-1-yl)-2H-pyrazol-3-yl]- (2-phenyl-quinazolin-4-yl)-amine (III-77): mp 169-170°C; ¹H

NMR (DMSO-d₆) δ 1.86-1.97 (2H, m), 2.75 (2H, t), 3.30 (3H, s), 3.45 (2H, t), 6.80 (1H, s), 7.50-7.60 (4H, m), 7.80-7.90 (2H, m), 8.45-8.55 (2H, m), 8.67 (1H, d), 10.30 (1H, s), 12.25 (1H, s); IR (solid) 1620, 1591, 1572, 1532, 5 1476, 1425, 1408, 1373, 1326, 1117, 1003, 831, 764, 714, 695; MS 360.3 (M+H)⁺.

Example 307 [5-(3-Benzylxyprop-1-yl)-2H-pyrazol-3-yl]-(2-phenyl-quinazolin-4-yl)-amine (III-78): mp 177-178°C; 10 ¹H NMR (DMSO) δ 1.92-2.03 (2H, m), 3.76-3.85 (2H, m), 3.52-3.62 (2H, m), 4.51 (2H, s), 6.82 (1H, s), 7.28-7.40 (5H, m), 7.46-7.58 (4H, m), 7.80-7.85 (2H, m), 8.47-8.52 (2H, m), 8.66 (1H, d), 10.45 (1H, s); IR (solid) 1621, 1591, 1562, 1532, 1479, 1454, 1426, 1408, 1374, 1101, 15 1006, 835, 766, 738, 712, 696; MS 436.3 (M+H)⁺.

Example 308 [5-(3-Aminoprop-1-yl)-2H-pyrazol-3-yl]-(2-phenyl-quinazolin-4-yl)-amine (III-79): A solution of [5-(3-tert-butoxycarbonylaminoprop-1-yl)-2H-pyrazol-3-yl]-(2-phenyl-quinazolin-4-yl)-amine (III-80) (250mg, 0.56mmol), in dichloromethane (3mL) at 0°C was treated with TFA (2mL). The mixture was warmed to room temperature then concentrated in vacuo. The residue was triturated and concentrated from dichloromethane (3x5mL) 20 and ether, then triturated with dichloromethane to crystallize the TFA salt. The resulting solid was collected by filtration and dissolved in a mixture of ethanol (3mL) and water (3mL). Potassium carbonate was added in portions to achieve pH 8 then the mixture 25 allowed to crystallize. The product was collected by filtration and dried at 80°C under vacuum to afford III-79 as an off-white powder (122mg, 63%): mp 205-207°C; ¹H NMR (DMSO) δ 1.68-1.83 (2H, m), 2.65-2.80 (4H, m), 6.80 (1H, 30

s), 7.50-7.60 (4H, m), 7.80-7.90 (2H, m), 8.45-8.53 (2H, m), 8.65 (1H, d), 10.45 (1H, br s); IR (solid) 1621, 1598, 1568, 1533, 1484, 1414, 1364, 1327, 1169, 1030, 951, 830, 776, 764, 705, 677; MS 345.3 (M+H)⁺.

5

Example 309 [5-(3-tert-Butoxycarbonylaminoprop-1-yl)-2H-pyrazol-3-yl]-(2-phenyl-quinazolin-4-yl)-amine (III-80): mp 199-200°C; ¹H NMR (DMSO) δ 1.37 (9H, s), 1.71-1.82 (2H, m), 2.67 (2H, t), 3.00-3.11 (2H, m), 7.81 (1H, s), 10 7.99 (1H, s), 7.50-7.60 (4H, m), 7.80-7.85 (2H, m), 8.48-8.52 (2H, m), 8.63 (1H, d), 10.40 (1H, s), 12.26 (1H, m); IR (solid) 2953, 1687, 1622, 1594, 1573, 1535, 1481, 1441, 1419, 1364, 1327, 1281, 1252, 1166, 1070, 1028, 998, 951, 848, 807, 768, 740, 728, 710, 693; MS 445.3 15 (M+H)⁺.

Example 310 5-Isopropylcarbamoyl-2H-pyrazol-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (III-81): ¹H NMR (500MHz, DMSO-d₆) δ 1.20 (d, J = 6.6 Hz, 6H), 4.13 (m, 1H), 7.42 (br. s, 1H), 7.61 (dd, J = 7.0, 7.7 Hz, 2H), 7.66 (t, J = 7.1 Hz, 1H), 7.71 (m, 1H), 7.99 (m, 2H), 8.39 (m, 1H), 8.42 (d, J = 7.1 Hz, 2H), 8.74 (d, J = 8.2 Hz, 1H), 11.41 (br. s, 1H); EI-MS 373.2 (M+H); HPLC-Method C, R_t 14.09 min.

25

Example 311 (5-Allylcarbamoyl-2H-pyrazol-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (III-82): ¹H NMR (500MHz, DMSO-d₆) δ 4.02 (m, 2H), 5.15 (m, 1H), 5.23 (m, 1H), 5.94 (m, 1H), 7.45 (br. s, 1H), 7.60 (t, J = 6.9 Hz, 2H), 7.64 (m, 1H), 30 7.72 (m, 1H), 7.98 (m, 2H), 8.43 (m 2H), 8.72 (d, J = 8.2 Hz, 1H), 8.84 (br. s, 1H), 11.34 (br. s, 1H); EI-MS 371.2 (M+H); HPLC-Method C, R_t 13.67 min.

Example 312 [5-(2-Methoxyethylcarbamoyl)-2H-pyrazol-3-yl]- (2-phenyl-quinazolin-4-yl)-amine (III-83): ^1H NMR (500MHz, DMSO-d6) δ 3.32 (s, 3H), 3.48 (m, 4H), 7.36 (br. s, 1H), 7.62 (m, 2H), 7.63 (m, 1H), 7.71 (m, 1H), 7.98 (m, 2H), 8.41 (dd, J = 1.4, 7.0, 2H), 8.70 (m, 2H), 11.30 (br. s, 1H); EI-MS 389.2 (M+H); HPLC-Method C, R_t 12.37 min.

Example 313 (5-Benzylcarbamoyl-2H-pyrazol-3-yl)- (2-phenyl-quinazolin-4-yl)-amine (III-84): ^1H NMR (500MHz, DMSO-d6) δ 4.52 (d, J = 6.0 Hz, 2H), 7.29 (m, 1H), 7.38 (d, J = 4.2 Hz, 4H), 7.58 (t, J = 7.5 Hz, 2H), 7.63 (m, 1H), 7.72 (m, 1H), 7.98 (m, 2H), 8.43 (d, J = 7.7 Hz, 2H), 8.72 (d, J = 7.5 Hz, 1H), 9.23 (br. s, 2H), 11.34 (br. s, 1H); EI-MS 421.2 (M+H); HPLC-Method C, R_t 16.76 min.

Example 314 (5-Cyclohexylcarbamoyl-2H-pyrazol-3-yl)- (2-phenyl-quinazolin-4-yl)-amine (III-85): ^1H NMR (500MHz, DMSO-d6) δ 1.16 (m, 1H), 1.34 (m, 4H), 1.62 (d, J = 2.6 Hz, 1H), 1.76 (m, 2H), 1.85 (m, 2H), 3.79 (m, 1H), 7.43 (m, 1H), 7.60 (t, J = 7.2 Hz, 2H), 7.65 (t, J = 7.1 Hz, 1H), 7.71 (ddd, J = 2.2, 5.4, 8.2 Hz, 1H), 7.98 (m, 2H), 8.35 (m, 1H), 8.43 (dd, J = 1.4, 7.2 Hz, 2H), 8.72 (d, J = 8.2 Hz, 1H), 11.34 (br. s, 1H); EI-MS 413.5 (M+H); HPLC-Method C, R_t 17.18 min.

Example 315 (5-Diethylcarbamoyl-2H-pyrazol-3-yl)- (2-phenyl-quinazolin-4-yl)-amine (III-86): ^1H NMR (500MHz, DMSO-d6) δ 1.18 (br. s, 3H), 1.25 (br. s, 3H), 3.49 (br. s, 2H), 3.69 (b. s, 2H), 7.21 (s, 1H), 7.59 (t, J = 6.9 Hz, 2H), 7.62 (m, 1H), 7.70 (m, 1H), 7.96 (m, 2H), 8.39

(d, $J = 7.1$ Hz, 2H), 8.74 (d, $J = 8.4$ Hz, 1H), 11.37 (br. s, 1H); EI-MS 387.2 (M+H); HPLC-Method C, R_t 14.50 min.

Example 316 [5-(Benzyl-methyl-carbamoyl)-2H-pyrazol-3-yl]- (2-phenyl-quinazolin-4-yl)-amine (III-87): 1 H NMR (500MHz, DMSO-d6) δ 3.33 (s, 3H), 4.75 (s, 2H), 7.26 (m, 1H), 7.31 (m, 1H), 7.38 (m, 4H), 7.58 (m, 2H), 7.70 (m, 1H), 7.95 (m, 3H), 8.26 (m, 1H), 8.40 (d, $J = 7.8$ Hz, 2H), 8.75 (m, 1H), 11.2 (br. s, 1H); EI-MS 435.2 (M+H); HPLC-Method C, R_t 16.77 min.

Example 317 (2-Phenyl-quinazolin-4-yl)-(5-propylcarbamoyl-2H-pyrazol-3-yl)-amine (III-88): 1 H NMR (500MHz, DMSO-d6) δ 0.94 (t, $J = 7.3$ Hz, 3H), 1.57 (m, 2H), 3.24 (q, $J = 6.5$ Hz, 2H), 7.39 (br. s, 1H), 7.60 (t, $J = 7.3$ Hz, 2H), 7.64 (m, 1H), 7.71 (br. t, $J = 6.5$ Hz, 1H), 7.98 (m, 2H), 8.42 (d, $J = 7.2$ Hz, 2H), 8.61 (br. s, 1H), 8.72 (d, $J = 8.5$ Hz, 1H), 11.34 (br. s, 1H); EI-MS 373.3 (M+H); HPLC-Method C, R_t 13.51 min.

Example 318 [5-(Ethyl-isopropyl-carbamoyl)-2H-pyrazol-3-yl]- (2-phenyl-quinazolin-4-yl)-amine (III-89): 1 H NMR (500MHz, DMSO-d6) δ 0.92 (t, $J = 7.4$ Hz, 6H), 1.52 (m, 2H), 1.59 (m, 1H), 3.79 (m, 2H), 7.53 (br. s, 1H), 7.57 (t, $J = 7.5$ Hz, 2H), 7.65 (t, $J = 7.2$ Hz, 1H), 7.71 (m, 1H), 7.99 (m, 2H), 8.23 (br. d, $J = 8.8$ Hz, 1H), 8.46 (d, $J = 7.5$ Hz, 2H), 8.74 (d, $J = 8.4$ Hz, 1H), 11.34 (br. s, 1H); EI-MS 401.2 (M+H); HPLC-Method C, R_t 15.51 min.

Example 319 (5-Cyclopropylcarbamoyl-2H-pyrazol-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (III-90): 1 H NMR (500MHz, DMSO-d6) δ 0.60 (m, 2H), 0.74 (m, 2H), 2.86 (m, 1H), 7.34 (br. s, 1H), 7.62 (m, 3H), 7.70 (m, 1H), 7.97 (m, 2H),

8.41 (d, $J = 7.9$ Hz, 2H), 8.63 (br. s, 1H), 8.72 (d, $J = 7.8$ Hz, 1H), 11.35 (br. s, 1H); EI-MS 371.2 (M+H); HPLC-Method C, R_t 12.64 min.

5 Example 320 (5-Isobutylcarbamoyl-2H-pyrazol-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (III-91): 1 H NMR (500MHz, DMSO-d6) δ 0.94 (d, $J = 6.7$ Hz, 6H), 1.88 (m, 1H), 3.12 (t, $J = 6.4$ Hz, 2H), 7.45 (br. s, 1H), 7.58 (t, $J = 7.2$ Hz, 3H), 7.64 (t, $J = 7.1$ Hz, 1H), 7.71 (m, 1H), 7.98 (m, 2H), 8.44 (dd, $J = 1.3, 7.9$ Hz, 2H), 8.62 (br. s, 1H), 8.72 (d, $J = 8.3$ Hz, 1H), 11.33 (br. s, 1H); EI-MS 387.2 (M+H); HPLC-Method C, R_t 14.70 min.

15 Example 321 {5-[(3S)-3-Methoxymethyl-pyrrolidine-1-carbonyl]-2H-pyrazol-3-yl}-(2-phenyl-quinazolin-4-yl)-amine (III-93): 1 H NMR (500MHz, DMSO-d6) δ 2.00 (m, 2H), 2.12 (m, 1H), 3.29 (s, 3H), 3.45 (t, $J = 8.7$ Hz, 1H), 3.57 (dd, $J = 3.2, 9.3$ Hz, 1H), 3.86 (m, 1H), 3.92 (m, 1H), 4.36 (m, 2H), 7.45 (br. s, 1H), 7.59 (t, $J = 7.2$ Hz, 2H), 7.63 (m, 1H), 7.69 (m, 1H), 7.97 (m, 2H), 8.40 (d, $J = 7.5$ Hz, 2H), 8.74 (d, $J = 7.6$ Hz, 1H), 11.38 (br. s, 1H); EI-MS 429.2 (M+H); HPLC-Method C, R_t 13.84 min.

25 Example 322 (2-Phenyl-quinazolin-4-yl)-(5-m-tolylcarbamoyl-2H-pyrazol-3-yl)-amine (III-94): 1 H NMR (500MHz, DMSO-d6) δ 2.33 (s, 3H), 6.97 (d, $J = 7.5$ Hz, 1H), 7.27 (t, $J = 7.8$ Hz, 1H), 7.62 (m, 7H), 7.72 (m, 1H), 7.98 (m, 2H), 8.46 (dd, $J = 2.0, 7.9$ Hz, 2H), 8.71 (m, 1H), 10.29 (s, 1H), 11.31 (br. s, 1H); EI-MS 421.2 (M+H); HPLC-Method C, R_t 17.11 min.

30 Example 323 (2-Phenyl-quinazolin-4-yl)-(5-p-tolylcarbamoyl-2H-pyrazol-3-yl)-amine (III-95): 1 H NMR

(500MHz, DMSO-d6) δ 2.30 (s, 3H), 7.20 (d, J = 8.3 Hz, 2H), 7.62 (m, 5H), 7.68 (d, J = 8.3 Hz, 2H), 7.72 (m, 1H), 7.98 (m, 2H), 8.46 (dd, J = 1.8, 7.0 Hz, 2H), 8.72 (m, 1H), 10.31 (s, 1H), 11.36 (br. s, 1H); EI-MS 421.2
5 (M+H); HPLC-Method C, R_t 16.95 min.

Example 324 (5-Methylcarbamoyl-2H-pyrazol-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (III-96): ¹H NMR (500MHz, DMSO-d6) δ 2.82 (d, J = 4.6 Hz, 3H), 7.31 (br. s, 1H), 7.62 (m, 3H), 7.69 (m, 1H), 7.97 (m, 2H), 8.42 (d, J = 7.1 Hz, 2H), 8.59 (br. s, 1H), 8.71 (d, J = 8.0 Hz, 1H), 11.30 (br. s, 1H); EI-MS 345.1 (M+H); HPLC-Method C, R_t 11.02 min.

15 Example 325 [5-(Morpholine-4-carbonyl)-2H-pyrazol-3-yl]-(2-phenyl-quinazolin-4-yl)-amine (III-97): ¹H NMR (500MHz, DMSO-d6) δ 3.33 (m, 4H), 3.83 (m 4H), 7.34 (br. s, 1H), 7.53 (m, 4H), 7.86 (m, 2H), 8.43 (m, 2H), 8.67 (d, J = 8.6 Hz, 1H), 10.70 (s, 1H), 13.56 (s, 1H); EI-MS 401.2
20 (M+H); HPLC-Method A, R_t 2.68 min.

Example 326 [5-(1-Methylpiperazine-4-carbonyl)-2H-pyrazol-3-yl]-(2-phenyl-quinazolin-4-yl)-amine (III-98):
¹H NMR (500MHz, DMSO-d6) δ 2.25 (s, 3H), 2.43 (m, 4H), 3.87 (m 4H), 7.33 (br. s, 1H), 7.53 (m, 4H), 7.87 (m, 2H), 8.45 (m, 2H), 8.67 (d, J = 7.6 Hz, 1H), 10.70 (s, 1H), 13.30 (s, 1H); EI-MS 414.2 (M+H); HPLC-Method A, R_t 2.38 min.

30 Example 327 [5-(2-Hydroxyethylcarbamoyl)-2H-pyrazol-3-yl]-(2-phenyl-quinazolin-4-yl)-amine (III-99): ¹H NMR (500MHz, DMSO-d6) δ 3.36 (m, 2H), 3.52 (m, 2H), 4.79 (m, 1H), 7.50 (m, 5H), 7.83 (m, 2H), 8.50 (m, 4H), 10.52 (br. s, 1H),

13.25 (s, 1H); EI-MS 375.1 (M+H); HPLC-Method A, R_t 2.51 min.

Example 328 (5-Carbamoyl-2*H*-pyrazol-3-yl)- (2-phenyl-5 quinazolin-4-yl)-amine (III-100): To a solution of 5-(2-phenyl-quinazolin-4-ylamino)-1*H*-pyrazole-3-carboxylic acid 2,5-dioxo-pyrrolidin-1-yl ester (270 mg, 0.63 mmol) in DMF (20 ml) was added a solution of ammonia in 1,4-dioxane (0.5 M, 10 ml). The resulting mixture was 10 stirred at room temperature for 24 h. After concentration of the solvents, the residue was added to water (20 ml). The resulting precipitate was collected to afford III-100 (168 mg, 80%) as a yellow solid. ¹H NMR (500MHz, DMSO-d6) δ 7.77-7.51 (m, 6H), 7.86 (br s, 2H), 8.11 (m, 1H), 8.50 (m, 2H), 8.63 (m, 1H), 10.52 (s, 1H), 15 11.25 (s, 1H); EI-MS 331.1 (M+H); HPLC-Method A, R_t 2.52 min.

Example 329 (4-Bromo-2*H*-pyrazol-3-yl)- (2-phenyl-20 quinazolin-4-yl)-amine (III-101): Prepared according to Method A to afford a yellow solid, mp 189°C; ¹H NMR (DMSO-d6) δ 7.44-7.46 (3H, m), 7.58 (1H, m), 7.87 (2H, d), 8.15 (1H, s), 8.31-8.34 (2H, m), 8.49 (1H, d), 10.08 (1H, s), 13.13 (1H, s); IR (solid) 3286, 2969, 1738, 1632; MS 25 366.2/368.2 (M+H)⁺.

Example 330 (4-Bromo-5-methyl-2*H*-pyrazol-3-yl)- (2-phenyl-quinazolin-4-yl)-amine (III-102): mp 183-185°C; ¹H NMR (DMSO) δ 2.33 (3H, br s), 7.44-7.46 (3H, m), 7.57 (1H, m), 7.84-7.87 (2H, m), 8.31-8.34 (2H, m), 8.48 (1H, d), 10.05 (1H, s), 12.91 (1H, br s); IR (solid) 3362, 3065, 2831, 1619, 1578; MS 380.2/382.2 (M+H)⁺.

Example 331 (4-Cyano-2H-pyrazol-3-yl)- (2-phenyl-quinazolin-4-yl)-amine (III-103): mp >250°C; ¹H NMR (DMSO) δ 7.47-7.49 (3H, m), 7.64 (1H, m), 7.91 (2H, m), 8.40-8.43 (2H, m), 8.53 (1H, d), 8.71 (1H, d), 10.61 (1H, s), 13.60 (1H, s); IR (solid) 3277, 3069, 2855, 2231, 1625; MS 313.2 (M+H)⁺.

Example 332 (5-Methyl-2H-pyrazol-3-yl)- (2-morpholin-4-yl-quinazolin-4-yl)-amine (III-104): mp 223-224°C; ¹H NMR (DMSO) δ 2.26 (3H, s), 3.65 (4H, m), 3.75 (4H, m), 6.44 (1H, s), 7.12 (1H, d), 7.33 (1H, d), 7.56 (1H, t), 8.37 (1H, d), 10.01 (1H, s), 12.13 (1H, br s); IR (solid) 1621, 1578, 1537, 1475, 1434, 1385; MS 311.0 (M+H)⁺.

Example 333 (5-Methyl-2H-pyrazol-3-yl)- (2-piperazin-1-yl-quinazolin-4-yl)-amine (III-105): mp 179-181°C; ¹H NMR (DMSO) δ 2.26 (3H, s), 2.74 (4H, br s), 3.71 (4H, br s), 6.43 (1H, s), 7.08 (1H, t), 7.30 (1H, d), 7.53 (1H, t), 8.34 (1H, d), 9.50 (1H, s), 12.08 (1H, br s); IR (solid) 2853, 1619, 1603, 1566, 1549, 1539; MS 310.0 (M+H)⁺

Example 334 [2-(4-Methylpiperidin-1-yl)-quinazolin-4-yl]- (5-methyl-2H-pyrazol-3-yl)-amine (III-106): mp 148-150°C; ¹H NMR (DMSO) δ 1.06 (3H, d), 1.03 (2H, m), 1.51-1.70 (3H, m), 2.26 (3H, s), 2.86 (2H, m), 4.73 (2H, d), 6.44 (1H, s), 7.06 (1H, d), 7.29 (1H, d), 7.52 (1H, t), 8.32 (1H, d), 9.92 (1H, s), 12.09 (1H, br s); IR (solid) 2917, 2840, 1629, 1593, 1562, 1546, 1486; MS 323.0 (M+H)⁺.

Example 335 [2-(4-Methylpiperazin-1-yl)-quinazolin-4-yl]- (5-methyl-2H-pyrazol-3-yl)-amine (III-107): mp 105-107°C; ¹H NMR (DMSO) δ 2.21 (3H, s), 2.26 (3H, s), 2.34 (4H, m), 3.75 (4H, m), 6.45 (1H, s), 7.09 (1H, t), 7.31 (1H, d),

7.54 (1H, t), 8.34 (1H, d), 9.96 (1H, s), 12.12 (1H, br s);
IR (solid) 2934, 2844, 2804, 1620, 1593, 1572, 1536,
1476; MS 324.0 (M+H)⁺.

5 Example 336 (5-Methyl-2H-pyrazol-3-yl)-[2-piperidin-1-yl-
quinazolin-4-yl]-amine (III-108): mp 294°C; ¹H NMR (DMSO)
δ 1.45-1.58 (4H, m), 1.63 (2H, m), 2.26 (3H, s), 3.79
(4H, m), 6.45 (1H, br s), 7.06 (1H, t), 7.29 (1H, d),
7.52 (1H, t), 8.33 (1H, d), 9.92 (1H, s), 12.11 (1H, br
10 s); IR (solid) 2929, 2847, 1632, 1591, 1500, 1482, 1437,
1382; MS 309.3 (M+H)⁺.

15 Example 337 (2-Azepan-1-yl)-quinazolin-4-yl]-[5-methyl-
2H-pyrazol-3-yl]-amine (III-109): mp 269°C; ¹H NMR (DMSO)
δ 1.50 (4H, br s), 1.76 (4H, br s), 2.25 (3H, s), 3.78
(4H, t), 6.55 (1H, br s), 7.03 (1H, t), 7.28 (1H, d),
7.50 (1H, t), 8.33 (1H, d), 9.92 (1H, s), 12.09 (1H, br
s); IR (solid) 3427, 2963, 2927, 2909, 2872, 2850, 1623,
1595, 1586, 1568, 1504, 1486, 1468, 1386, 1427; MS 323.3
20 (M+H)⁺.

25 Example 338 [2-(4-(2-Hydroxyethylpiperidin-1-yl)-
quinazolin-4-yl]-[5-methyl-2H-pyrazol-3-yl]-amine (III-
110): mp 175°C; ¹H NMR (DMSO) δ 1.08 (2H, m), 1.38 (2H,
m), 1.57-1.83 (3H, m), 2.26 (3H, s), 2.85 (2H, t), 3.47
(2H, m), 4.38 (1H, t), 4.75 (2H, d), 6.45 (1H, br s),
7.06 (1H, t), 7.29 (1H, d), 7.52 (1H, t), 8.32 (1H, d),
9.93 (1H, s), 12.12 (1H, br s); IR (solid) 3365, 3073,
2972, 2868, 1622, 1604, 1586, 1568, 1486, 1463, 1440,
30 1394; MS 353.2 (M+H)⁺.

Example 339 (5-Cyclopropyl-2H-pyrazol-3-yl)-[2-(4-
methylpiperidin-1-yl)-quinazolin-4-yl]-amine (III-111):

To a solution of (5-cyclopropyl-1H-pyrazol-3-yl)-(2-chloro-quinazolin-4-yl)-amine (118 mg, 0.41 mmol) in tert-butanol (3.0 mL) was added 4-methylpiperidine (0.49 mL, 4.1 mmol) and the reaction mixture heated at reflux 5 overnight. The reaction mixture was concentrated *in vacuo* and the residue dissolved in a mixture EtOH:water (1:3, 4 mL). Potassium carbonate (57mg, 0.41 mmol) was added and the mixture stirred at room temperature for 2 hours. The resulting suspension was filtered, washed 10 with water (x2), and rinsed with Et₂O (x2) to afford III-111 as a white solid (123mg, 85%): mp 190°C; ¹H NMR (DMSO) δ 0.66 (2H, s), 0.93 (5H, br s), 1.07 (2H, d), 1.66 (3H, s), 1.91 (1H, s), 2.85 (2H, t), 4.72 (2H, d), 6.33 (1H, s), 7.06 (1H, t), 7.29 (1H, d), 7.52 (1H, t), 8.31 (1H, d), 9.95 (1H, s), 12.18 (1H, br s); IR (solid) 2925, 2852, 1622, 1590, 1581, 1558, 1494, 1481, 1453, 1435, 15 1394; MS 349.2 (M+H)⁺.

Example 340 [2-(1,4-Dioxa-8-aza-spiro[4,5]dec-8-yl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-112): mp 191°C; ¹H NMR (DMSO) δ 1.65 (4H, s), 2.26 (3H, s), 3.90 (4H, s), 3.93 (4H, s), 6.43 (1H, br s), 7.09 (1H, t), 7.32 (1H, d), 7.54 (1H, t), 8.35 (1H, d), 9.99 (1H, br s), 12.13 (1H, br s); IR (solid) 3069, 2964, 25 2927, 2868, 1618, 1581, 1568, 1540, 1495, 1481, 1435, 1390; MS 367.3 (M+H)⁺.

Example 341 [2-(4-Cyclopentylamino-piperidin-1-yl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-113): mp 191°C; ¹H NMR (DMSO) δ 1.33 (2H, d), 1.65 (4H, s), 1.87 (2H, d), 2.20 (1H, s), 2.26 (3H, s), 2.49 (2H, s), 3.00 (2H, t), 3.36 (2H, s), 4.61 (2H, d), 6.45 (1H, br s), 7.07 (1H, s), 7.31 (1H, d), 7.52 (1H, s), 8.33

(1H, d), 9.94 (1H, br s), 12.12 (1H, br s); IR (solid) 3371, 2943, 1622, 1600, 1581, 1545, 1509, 1463, 1440, 1390; MS 378.2 (M+H)⁺.

5 Example 342 [2-(4-Hydroxypiperidin-1-yl)-quinazolin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (III-114): mp 123°C; ¹H NMR (DMSO) δ 1.34 (2H, d), 1.80 (2H, d), 2.26 (3H, s), 3.24 (2H, t), 3.72 (1H, br s), 4.39 (2H, d), 4.70 (1H, d), 6.44 (1H, br s), 7.07 (1H, t), 7.30 (1H, d), 7.53 (1H, t), 8.33 (1H, d), 9.94 (1H, br s), 12.11 (1H, br s); IR (solid) 3265, 3151, 2927, 2863, 1622, 1600, 1572, 1540, 1504, 1476, 1440, 1390, 1349, 1066, 1098; MS 325.3 (M+H)⁺.

15 Example 343 (5-Cyclopropyl-2H-pyrazol-3-yl)-[2-(4-hydroxy-4-phenylpiperidin-1-yl)-quinazolin-4-yl]-amine (III-115): mp 131°C; ¹H NMR (DMSO) δ 0.64 (2H, q), 0.93 (2H, q), 1.68 (2H, d), 1.83-1.97 (3H, m), 3.20-3.45 (2H, m), 4.69 (2H, d), 5.11 (1H, s), 6.37 (1H, br s), 7.08 (1H, t), 7.20 (1H, t), 7.31 (3H, t), 7.49 (2H, d), 7.53 (1H, t), 8.33 (1H, d), 9.98 (1H, br s), 12.18 (1H, br s); IR (solid) 3362, 2952, 2934, 2911, 2870, 2825, 1618, 1584, 1570, 1559, 1536, 1481, 1459, 1431, 1372, 1336, 1213, 994; MS 427.6 (M+H)⁺.

25 Example 344 (5-Cyclopropyl-2H-pyrazol-3-yl)-[2-(1,3-dihydro-isoindol-2-yl)-quinazolin-4-yl]-amine (III-116): Prepared according to Method E-I to afford an off-white solid, mp 237°C; ¹H NMR (DMSO-d6) δ 0.79 (2H, s), 1.00 (2H, d), 1.99 (1H, m), 4.92 (4H, d), 6.72 (1H, br s), 7.13 (1H, t), 7.33 (2H, s), 7.30-7.48 (3H, m), 7.58 (1H, t), 8.40 (1H, d), 10.12 (1H, s), 12.17 (1H, s); IR (solid) 3449, 3318, 2850, 1623, 1595, 1577, 1541, 1509,

1482, 1432, 1391, 1359, 1141, 1027, 877, 814; MS 369.4
(M+H)⁺.

Example 345 (2-Azepan-1-yl)-quinazolin-4-yl]-[5-cyclopropyl-2H-pyrazol-3-yl]-amine (III-117): mp 199-200°C; ¹H NMR (DMSO-d₆) δ 0.60-0.70 (2H, m), 0.90-1.00 (2H, m), 1.45-1.57 (4H, m), 1.70-1.85 (4H, m), 1.88-1.97 (1H, m), 3.75-3.87 (4H, m), 6.42 (1H, s), 7.02 (1H, t), 7.27 (1H, d), 7.49 (1H, t), 8.29 (1H, d), 9.91 (1H, s), 12.19 (1H, br s); IR (solid) 2929, 1624, 1595, 1581, 1563, 1542, 1498, 1482, 1440, 1426, 1397, 1356, 1305, 1000, 825, 754; MS 349.2 (M+H)⁺.

Example 346 (5-Cyclopropyl-2H-pyrazol-3-yl)-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-quinazolin-4-yl]-amine (III-118): mp 182-184°C; ¹H NMR (DMSO) δ 0.75 (2H, d), 1.02 (2H, d), 1.96 (1H, m), 2.89 (2H, m), 4.05 (2H, m), 4.94 (2H, s), 6.46 (1H, s), 7.10 (1H, t), 7.21 (4H, d), 7.37 (1H, d), 7.55 (1H, d), 8.36 (1H, d), 10.05 (1H, s), 12.23 (1H, br s); IR (solid) 1621, 1581, 1560, 1537, 1479, 1456, 1426, 1396, 1374, 1341, 1222; MS 383.3 (M+H)⁺.

Example 347 (5-Cyclopropyl-2H-pyrazol-3-yl)-[2-(2,3-dihydro-indol-1-yl)-quinazolin-4-yl]-amine (III-119): mp 150-153°C; ¹H NMR (DMSO) δ 0.74 (2H, d), 0.98 (2H, d), 1.96 (1H, m), 3.15 (2H, t), 4.25 (2H, t), 6.45 (1H, br s), 6.88 (1H, t), 7.09 (1H, t), 7.20 (2H, m), 7.53 (1H, d), 7.65 (1H, t), 8.43 (2H, br s), 10.09 (1H, s), 12.28 (1H, br s); IR (solid) 1621, 1588, 1577, 1564, 1537, 1487, 1455, 1425, 1386, 1259; MS 369.3 (M+H)⁺.

Example 348 (5-Cyclopropyl-2H-pyrazol-3-yl)-[2-(4-hydroxymethylpiperidin-1-yl)-quinazolin-4-yl]-amine (III-

120) : mp 142°C; ^1H NMR (DMSO) δ 0.67 (2H, d), 0.96 (2H, d), 1.10 (2H, q), 1.55-1.70 (3H, m), 1.91 (1H, m), 2.85 (2H, t), 3.28 (2H, s), 4.48 (1H, s), 4.76 (2H, d), 6.34 (1H, s), 7.06 (1H, t), 7.30 (1H, d), 7.52 (1H, t), 8.31 (1H, d), 9.96 (1H, s), 12.19 (1H, s); IR (solid) 3363, 3000, 2927, 2854, 1618, 1604, 1573, 1536, 1509, 1477, 1436, 1395, 1354, 1314, 1241, 1186, 1091, 995, 941, 823; MS 365.8 ($\text{M}+\text{H}$)⁺.

10 Example 349 (5-Cyclopropyl-2H-pyrazol-3-yl)-[2-(3,4-dihydro-2H-quinolin-1-yl)-quinazolin-4-yl]-amine (III-121) : mp 137-145°C; ^1H NMR (DMSO-d6) δ 0.55 (2H, d), 0.88 (2H, d), 1.78 (1H, m), 1.92 (2H, t), 2.75 (2H, t), 4.04 (2H, t), 6.20 (1H, br s), 6.97 (1H, t), 7.14 (1H, m), 7.19 (1H, t), 7.42 (1H, d), 7.61 (1H, t), 7.67 (1H, d), 8.43 (1H, d), 10.04 (1H, s), 12.21 (1H, br s); IR (solid) 1622, 1572, 1539, 1493, 1454, 1420, 1373, 1249; MS 383.3 ($\text{M}+\text{H}$)⁺.

20 Example 350 (5-Methoxycarbonyl-2H-pyrazol-3-yl)-[2-(piperidine-1-yl)-quinazolin-4-yl]-amine (III-122) : ^1H NMR (500MHz, CDCl₃) δ 1.7-1.8 (6H, m), δ 3.8 (4H, m), δ 3.9 (3H, s), δ 5.5 (1H, s), δ 7.15 (1H, t), δ 7.4 (1H, d), δ 7.6 (1H, t), δ 8.0 (1H, d). HPLC-Method B, (starting with 95% H₂O) R_t 7.4 min; MS (ES+) 353.24 ($\text{M}+\text{H}$).

30 Example 351 [5-(Piperidine-1-carbonyl)-2H-pyrazol-3-yl]-[2-(piperidine-1-yl)-quinazolin-4-yl]-amine (III-123) : HPLC-Method B, (starting with 95% H₂O:0.1% TFA) R_t 8.0 min; MS (ES+) 406.30, (ES-) 404.30.

30 Example 352 (5-Hydroxymethyl-2H-pyrazol-3-yl)-[2-(piperidin-1-yl)-quinazolin-4-yl]-amine (III-124) : To a

solution of III-122 (10.0 mg, 0.028 mmol) in THF (6 mL) at ambient temperature was slowly added a 1M solution of LiAlH₄ in THF (0.05 mL, 0.05 mmol). After 15 minutes the solution was quenched with water and 1N HCl. The product
5 was extracted from the aqueous layer with EtOAc. The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by preparatory HPLC to afford III-124 (4.0 mg, 44%). HPLC-Method B, (starting with 95% H₂O:0.1% TFA) R_t 6.1 min; MS
10 (ES+) 325.13 (M+H), (ES-) 323.13 (M-H).

Example 353 (5-Carbamoyl-2*H*-pyrazol-3-yl)-[2-(piperidin-1-yl)-quinazolin-4-yl]-amine (III-125): A solution of III-122 (1.5 g, 4.3 mmol) in 2.0 M NH₃/MeOH (100 mL) was
15 heated at 110°C for 2 days. The dark brown reaction mixture was concentrated in vacuo to afford a viscous oil which was purified by column chromatography to yield 0.7 g (50%) of III-125. ¹H NMR (500MHz, CD3OD-d₃) δ 1.6 (4H, m), δ 1.7 (2H, m), δ 3.3 (1H, s), δ 3.8 (4H, m), δ 5.5 (1H, s), δ 7.15 (1H, t), δ 7.45 (1H, d), δ 7.55 (1H, t), δ 8.0 (1H, d); HPLC-Method B, (starting with 95% H₂O:0.1% TFA) R_t 5.9 min; MS (ES+) 338.13, (ES-) 336.15.

Example 354 (5-Carbamoyl-2*H*-pyrazol-3-yl)-[2-(4-methylpiperidin-1-yl)-quinazolin-4-yl]-amine (III-126): HPLC-Method B, (starting with 95% H₂O:0.1% TFA) R_t 6.4 min; MS (ES+) 352.19, (ES-) 350.20.

Example 355 (5,7-Difluoro-1*H*-indazol-3-yl)-(2-phenyl-30 5,6,7,8-tetrahydroquinazolin-4-yl)-amine (III-127): ¹H NMR (500 MHz, DMSO-d₆) δ 13.7 (s, 1H), 10.3 (s, br, 1H), 7.90 (d, 2H), 7.52 (t, 1H), 7.45 (m, 3H), 7.26 (d, 1H), 2.99

(m, 2H), 2.75 (m, 2H), 1.95 (br, 4H) ppm; MS (ES+) 378.24 (M+H); (ES-) 376.23 (M-H); HPLC-Method A, R_t 3.04 min.

Example 356 (2-Phenyl-5,6,7,8-tetrahydroquinazolin-4-yl)-
5 (5-trifluoromethyl-1H-indazol-3-yl)-amine (III-128): ¹H NMR (500 MHz, DMSO-d6) δ 13.4 (s, 1H), 10.2 (s, br, 1H), 8.13 (s, 1H), 7.86 (d, 2H), 7.78 (d, 1H), 7.69 (d, 1H), 7.50 (t, 1H), 7.35 (dd, 2H), 2.89 (m, 2H), 2.72 (m, 2H), 1.90 (s, br, 4H) ppm; MS (ES+) 410.24 (M+H); (ES-) 408.23 (M-H); HPLC-Method A, R_t 3.19 min.

Example 357 (7-Fluoro-1H-indazol-3-yl)-(2-phenyl-
quinazolin-4-yl)-amine (III-129): ¹H NMR (500 MHz, DMSO-d6) δ 13.6 (s, 1H), 11.1 (s, br, 1H), 8.65 (d, 1H), 8.03 (d, 2H), 7.95 (s, 2H), 7.67 (m, 1H), 7.45 (m, 2H), 7.33 (t, 2H), 7.22 (dd, 1H), 6.99 (td, 1H) ppm. MS (ES+): m/e= 356.20 (M+H); HPLC-Method A R_t 3.00 min.

Example 358 (5-Fluoro-1H-indazol-3-yl)-(2-phenyl-
20 quinazolin-4-yl)-amine (III-130): ¹H NMR (500 MHz, DMSO-d6) δ 13.2 (s, 1H), 11.3 (s, br, 1H), 8.67 (d, 1H), 8.04 (d, 2H), 7.96 (s, 2H), 7.70 (m, 1H), 7.58 (dd, 1H), 7.43 (m, 4H), 7.28 (td, 1H) ppm. MS (ES+) 356.20 (M+H); HPLC-Method A, R_t 3.00 min.

25
Example 359 (5,7-Difluoro-1H-indazol-3-yl)-(2-phenyl-
quinazolin-4-yl)-amine (III-131): ¹H NMR (500 MHz, DMSO-d6) δ 13.7 (s, 1H), 8.65 (d, 1H), 8.04 (d, 2H), 7.95 (s, 2H), 7.68 (m, 1H), 7.45 (m, 1H), 7.35 (m, 4H) ppm. MS (ES+): m/e= 374.17 (M+H); HPLC-Method A, R_t 3.07 min.

Example 360 (1H-Indazol-3-yl)-[2-(3-trifluoromethyl-
phenyl)-quinazolin-4-yl]-amine (III-132): ¹H NMR (500MHz,

DMSO-d₆) δ 7.06 (t, 1H), 7.42 (t, 1H), 7.59 (d, 1H), 7.63 (t, 1H), 7.66 (d, 1H), 7.71 (m, 1H), 7.80 (d, 1H), 7.98 (m, 2H), 8.33 (s, 1H), 8.46 (d, 1H), 8.71 (d, 1H), 11.04 (br. s, 1H), 12.97 (s, 1H); EI-MS 406.1 (M+1); HPLC-
5 Method A, R_t 3.15 min.

Example 361 (2-Phenyl-quinazolin-4-yl)-[1H-pyrazolo[4,3-b]pyridin-3-yl]-amine (III-133): ¹H NMR (500 MHz, DMSO-d₆) δ 13.3 (s, br, 1H), 11.4 (s, br, 1H), 8.78 (d, 1H), 8.58 (dd, 1H), 8.24 (d, 1H), 8.10 (m, 2H), 7.95 (d, 2H), 7.86 (t, 1H), 7.56 (m, 2H), 7.44 (t, 2H) ppm. MS (ES+) 339.11 (M+H); HPLC-Method A, R_t 2.63 min.

Example 362 [5-(3-Methoxy-phenyl)-6-oxo-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl]-[2-phenyl-quinazolin-4-yl]-amine (III-134): ¹H NMR (500 MHz, MeOH-d₄) δ 8.65 (d, 1H), 8.17 (m, 3H), 8.10 (d, 1H), 7.90 (t, 1H), 7.75 (t, 1H), 7.58 (m, 2H), 7.25 (t, 1H), 6.95 (m, 2H), 6.85 (d, 1H), 6.80 (s, 1H), 3.64 (s, 3H) ppm. MS (ES+): m/e= 20 462.2 (M+H).

Example 363 (6-Oxo-5-phenyl-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl)-[2-phenyl-quinazolin-4-yl]-amine (III-135): ¹H NMR (500 MHz, MeOH-d₄) δ 8.61 (d, 1H), 8.13 (m, 3H), 8.05 (d, 1H), 7.85 (t, 1H), 7.70 (t, 1H), 7.58 (m, 2H), 7.32 (m, 5H), 6.79 (s, 1H) ppm. MS (ES+): m/e= 432.2 (M+H).

Example 364 [5-(4-Methoxy-phenyl)-6-oxo-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl]-[2-phenyl-quinazolin-4-yl]-amine (III-136): MS (ES+) 462.2 (M+H).

Example 365 [5-(2,4-Dichloro-phenyl)-6-oxo-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl]- (2-phenyl-quinazolin-4-yl)-amine (III-137) : ^1H NMR (500 MHz, MeOH-d4) δ 8.63 (d, 1H), 8.17 (m, 4H), 7.89 (t, 1H), 7.73 (t, 1H), 7.61 (t, 2H), 7.57 (d, 1H), 7.32 (m, 1H), 7.21 (d, 1H), 6.84 (s, 1H) ppm. MS (ES+) : m/e= 500.1 (M+H).

Example 366 [6-Oxo-5-(3-trifluoromethyl-phenyl)-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl]- (2-phenyl-quinazolin-4-yl)-amine (III-138) : ^1H NMR (500 MHz, MeOH-d4) δ 8.55 (d, 1H), 8.19 (d, 2H), 7.92 (m, 2H), 7.65 (m, 3H), 7.45 (t, 2H), 7.25 (t, 1H), 7.13 (t, 1H), 7.05 (t, 1H), 6.75 (s, 1H) ppm. MS (ES+) : m/e= 500.2 (M+H).

15 Example 367 [6-Oxo-5-(4-Phenoxy-phenyl)-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl]- (2-phenyl-quinazolin-4-yl)-amine (III-139) : MS (ES+) 524.3 (M+H).

20 Example 368 [5-(4-Chloro-phenyl)-6-oxo-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl]- (2-phenyl-quinazolin-4-yl)-amine (III-140) : MS (ES+) 466.2 (M+H).

Example 369 (2-imidazol-1-yl-quinazolin-4-yl)- (1H-indazol-3-yl)-amine (III-141) : ^1H NMR (500MHz, DMSO-d6) δ 7.10 (t, 1H), 7.44 (t, 1H), 7.50 (br. s, 1H), 7.60 (d, 1H), 7.72 (m, 2H), 7.77 (m, 1H), 7.88 (d, 1H), 7.98 (t, 1H), 8.73 (d, 1H), 8.96 (s, 1H), 11.23 (s, 1H), 13.06 (s, 1H); EI-MS 328.1 (M+1); HPLC-Method A, R_t 2.93 min.

30 Example 370 (1H-Indazol-3-yl)- [2-(2-methyl-imidazol-1-yl-quinazolin-4-yl)-amine (III-142) : ^1H NMR (500MHz, DMSO-d6) δ 2.48 (s, 3H), 7.10 (t, 1H), 7.43 (t, 1H), 7.57 (d, 1H), 7.60 (d, 1H), 7.67 (d, 1H), 7.76 (td, 1H), 7.86 (d, 1H),

7.91 (d, 1H), 8.01 (td, 1H), 8.72 (d, 1H), 11.15 (s, 1H),
13.10 (s, 1H); EI-MS 342.1 (M+1); HPLC-Method A, R_t 3.06
min.

5 Example 371 (*1H-Indazol-3-yl*) - (*2-piperidin-1-yl*-
 quinazolin-4-yl) - *amine* (III-143): ¹H NMR (500MHz, DMSO-d6)
 δ 1.48 (m, 6H), 3.60 (m, 4H), 7.11 (t, 1H), 7.52 (t, 1H),
 7.55 (d, 1H), 7.64 (d, 1H), 7.69 (d, 1H), 7.75 (d, 1H),
 7.90 (t, 1H), 8.58 (d, 1H), 11.82 (br. s, 1H), 13.25 (s,
10 1H); EI-MS 345.1 (M+1); HPLC-Method A, R_t 3.03 min.

Example 372 (*1H-Indazol-3-yl*) - [*2-(octahydro-quinolin-1-*
 yl)-quinazolin-4-yl] - *amine* (III-144): ¹H NMR (500MHz,
 DMSO-d6) δ 0.6-1.9 (m, 13 H), 3.15 (m, 1H), 3.25 (m, 1H),
15 4.0 (m, 1H), 7.10 (t, 0.5H), 7.12 (t, 0.5H), 7.55 (m,
 2H), 7.66 (d, 0.5 H), 7.69 (d, 0.5 H), 7.77 (d, 1H), 7.91
 (t, 1H), 8.55 (d, 0.5 H), 8.59 (d, 0.5 H), 11.46 (s, 0.5
 H), 11.54 (s, 0.5 H), 11.78 (s, 0.5 H), 11.84 (s, 0.5 H),
 13.10 (s, 0.5 H), 13.12 (s, 0.5 H); EI-MS 399.3 (M+1);
20 HPLC-Method A, R_t 3.37 min.

Example 373 (*1H-Indazol-3-yl*) - [*2-(2,6-dimethyl-morpholin-4-yl)-quinazolin-4-yl*] - *amine* (III-145): ¹H NMR (500MHz,
 DMSO-d6) δ 1.0 (m, 6H), 4.0 (m, 6H), 7.12 (t, 1H), 7.41
 (td, 1H), 7.56 (t, 1H), 7.58 (d, 1H), 7.68 (dd, 1H), 7.77
25 (t, 1H), 7.93 (t, 1H), 8.60 (d, 1H), 11.69 (s, 1H), 13.16
 (s, 1H); EI-MS 375.3 (M+1); HPLC-Method A, R_t 2.93 min.

Example 374 (*5-Methyl-2H-pyrazol-3-yl*) - (*2-phenyl-pyrimidin-4-yl*) - *amine* (IV-1): mp 245-246°C; ¹H NMR (DMSO)
 δ 2.26 (3H, s), 6.32 (1H, br s), 7.07 (1H, br s), 7.48-
 7.54 (3H, m), 8.33-8.39 (3H, m), 9.87 (1H, s), 12.03 (1H,

s); IR (solid) 1628, 1589, 1579, 1522, 1479, 1441, 1393, 1336; MS 252.2 (M+H)⁺.

Example 375 [6-(4-Acetamidophenylsulfanyl)-2-phenyl-pyrimidin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (IV-3):

A suspension of Fenclorim (4,6-dichloro-2-phenylpyrimidine) (0.1g, 0.44 mmol), 3-amino-5-methylpyrazole (0.045 g, 0.47 mmol), N, N-diisopropylethylamine (0.08 ml, 0.47 mmol) and sodium iodide (0.067 g, 0.44 mmol) in n-butanol (5 ml) were heated at 117 °C for 18 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography (silica gel, 3:2 Petrol:EtOAc) to afford 0.037 g (29 % yield) of (6-Chloro-2-phenyl-pyrimidin-4-yl)-(5-methyl-2H-pyrazol-3-yl)-amine as a off-white solid. A suspension of the above pyrimidine (0.037 g, 0.13 mmol) and thioacetamidothiophenol (0.108 g, 0.64 mmol) in *tert*-butanol was heated at 85 °C under nitrogen for 2 days. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The concentrate was dissolved in EtOAc, and washed with NaHCO₃ (sat, aq.). The organic layer is concentrated *in vacuo*, and the crude product by preperative HPLC. The residual disulfide that still remained in the mixture after HPLC may be removed by precipitation from EtOAc and filtration. The mother liquor was concentrated to afford IV-3 (7mg, 13 % yield) as an off-white solid: mp 235-236°C; ¹H NMR (DMSO) δ 2.10 (3H, s), 2.21 (3H, s), 6.33 (1H, br s), 7.50 (3H, m), 7.7-7.59 (2H, m), 7.76-7.78 (2H, m), 8.25 (2H, m), 9.72, 10.26 and 11.93 (3 H, 3 x br s); IR (solid) 1669, 1585, 1551, 1492, 1392, 1372, 1312, 1289, 1259, 1174, 1102, 1089, 1027, 1015, 984; MS 417.3 (M+H)⁺.

Example 376 [2-(4-Methylpiperidin-1-yl)-pyrimidin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (IV-4): mp 215-216°C; ^1H NMR (CD_3OD) δ 0.96 (3H, d), 1.16 (2H, m), 1.66 (3H, m), 5 2.27 (3H, s), 2.86 (2H, t), 4.58 (2H, m), 4.78 (2H, exch. protons), 6.13 (2H, m), 7.83 (1H, d); IR (solid) 1593, 1550, 1489, 1436, 1331, 1246, 1231; MS 273.1 ($\text{M}+\text{H})^+$.

Example 377 [2-(4-Methylpiperidin-1-yl)-5-nitropyrimidin-10 4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (IV-5): mp 185-187°C; ^1H NMR (DMSO) δ 0.93 (3H, d), 1.06-1.18 (2H, m), 1.68-1.80 (3H, m), 2.26 (3H, s), 3.01-3.12 (2H, m), 4.63 (1H, d), 4.80 (1H, d), 6.39 (1H, s), 9.00 (1H, s), 10.41 (1H, s), 12.36 (1H, s); IR (solid) 1589, 1517, 1479, 15 1446, 1346, 1317, 1246, 1222, 1055; MS 318.2 ($\text{M}+\text{H})^+$.

Example 378 [5-Amino-2-(4-Methylpiperidin-1-yl)-pyrimidin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (IV-6): To a solution of IV-5 (48 mg, 0.151 mmol) in ethanol (2.0 mL) was added tin dichloride dihydrate (171 mg, 0.756 mmol) and the resulting mixture heated at reflux for 3 hours. The reaction was cooled to room temperature and poured onto a mixture of 1M NaOH:dichloromethane:propanol (18:8:4mL) and stirred for 15 minutes. The layers were 20 separated and the aqueous layer extracted twice with dichloromethane. The combined organic layers were concentrated *in vacuo* and the residue purified by flash chromatography (silica gel, gradient dichloromethane:MeOH) to afford IV-6 as a grey solid (27mg, 63%): ^1H NMR (DMSO) δ 0.88-1.04 (5H, m), 1.55-1.62 (3H, m), 2.21 (3H, s), 2.70 (2H, m), 3.36 (2H, m), 4.40 (2H, m), 6.37 (1H, s), 7.49 (1H, s), 8.40 (1H, s), 11.92 (1H, br s); MS 288.2 ($\text{M}+\text{H})^+$.

Example 379 [5-Amino-6-methyl-2-(4-methylpiperidin-1-yl)-pyrimidin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (IV-7):
mp 172-175°C; ^1H NMR (DMSO) δ 0.90 (3H, d), 1.03 (2H, m),
5 1.52-1.62 (3H, m). 2.13 (3H, s), 2.20 (3H, s), 2.69 (2H,
m), 3.92 (2H, br s), 4.44 (2H, d), 6.35 (1H, s), 8.41
(1H, s), 11.85 (1H, br s); IR (solid) 1612, 1589, 1489,
1446, 1317; MS 302.5 ($\text{M}+\text{H}$)⁺.

10 Example 380 [6-Methyl-2-(4-methyl-phenyl)-pyrimidin-4-yl]-(5-phenyl-2H-pyrazol-3-yl)-amine (IV-10): MS 342.34
($\text{M}+\text{H}$); HPLC-Method E, R_t 1.334 min.

15 Example 381 [2-(4-Chloro-phenyl)-6-methyl-pyrimidin-4-yl]-(5-furan-2-yl-2H-pyrazol-3-yl)-amine (IV-11): MS
352.11 ($\text{M}+\text{H}$); HPLC Method E, R_t 1.194 min.

20 Example 382 5-Furan-2-yl-2H-pyrazol-3-yl)-(6-methyl-2-phenyl-pyrimidin-4-yl)-amine (IV-12): MS 318.21 ($\text{M}+\text{H}$);
HPLC-Method E, 1.192 min.

25 Example 383 [6-Methyl-2-(4-trifluoromethyl-phenyl)-pyrimidin-4-yl]-(5-phenyl-2-yl-2H-pyrazol-3-yl)-amine (IV-13): MS 396.24 ($\text{M}+\text{H}$); HPLC-Method E, R_t 1.419 min.

Example 384 (5-Furan-2-yl-2H-pyrazol-3-yl)-[6-methyl-2-(4-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine (IV-14):
MS 386.08 ($\text{M}+\text{H}$); HPLC-Method E 1.347 min.

30 Example 385 [2-(2,3-Dihydro-benzo[1,4]dioxin-2-yl)-6-methyl-pyrimidin-4-yl]-(5-furan-2-yl-2H-pyrazol-3-yl)-amine (IV-15): MS 376.18 ($\text{M}+\text{H}$); HPLC-Method E, R_t 1.181 min.

Example 386 [2-(2,3-Dihydro-bezo[1,4]dioxin-2-yl)-6-ethyl-pyrimidin-4-yl]- (5-methyl-2H-pyrazol-3-yl)-amine (IV-16) : MS 338.17 (M+H) ; HPLC-Method E, R_t 1.082 min.

5

Example 387 (6-Ethyl-2-phenyl-pyrimidin-4-yl)- (5-methyl-2H-pyrazol-3-yl)-amine (IV-17) : MS 280.18 (M+H) ; HPLC-Method E, R_t 1.024 min.

10 Example 388 (6-Methyl-2-phenyl-pyrimidin-4-yl)- (5-phenyl-2H-pyrazol-3-yl)-amine (IV-19) : MS 328.51 (M+H) ; HPLC-Method E, R_t 1.192 min.

15 Example 389 [6-Ethyl-2-(4-trifluoromethyl-phenyl)-pyrimidin-4-yl]- (5-methyl-2H-pyrazol-3-yl)-amine (IV-20) : MS 348.5 (M+H) ; HPLC-Method E, R_t 1.224 min.

20 Example 390 (5-Furan-2-yl-2H-pyrazol-3-yl)- [6-methyl-2-(4-methyl-phenyl)-pyrimidin-4-yl]-amine (IV-21) : MS 332.23 (M+H) ; HPLC-Method E, R_t 1.139 min.

Example 391 (6-Methoxymethyl-2-phenyl-pyrimidin-4-yl)- (5-methyl-2H-pyrazol-3-yl)-amine (IV-22) : MS 296.31 (M+H) ; HPLC-Method E, R_t 0.971 min.

25

Example 392 (5,6-Dimethyl-2-phenyl-pyrimidin-4-yl)- (5-methyl-2H-pyrazol-3-yl)-amine (IV-23) : MS 280.2 (M+H) ; HPLC-Method E, R_t 0.927 min.

30 Example 393 (6-Methyl-2-phenyl-pyrimidin-4-yl)- (5-methyl-2H-pyrazol-3-yl)-amine (IV-24) : MS 266.18 (M+H) ; HPLC-Method E, R_t 0.925 min.

Example 394 [6-Ethyl-2-(4-methyl-phenyl)-pyrimidin-4-yl]-
(5-methyl-2H-pyrazol-3-yl)-amine (IV-25) : MS 294.46
(M+H) ; HPLC-Method E, R_t 1.174 min.

5 Example 395 [2-(4-Chloro-phenyl)-6-ethyl-pyrimidin-4-yl]-
(5-methyl-2H-pyrazol-3-yl)-amine (IV-26) : MS 314.42
(M+H) ; HPLC-Method E R_t 1.213 min.

10 Example 396 (5-Methyl-1H-pyrazol-3-yl)-(6-methyl-2-p-
tolyl-pyrimidin-4-yl)-amine (IV-27) : MS 280.45 (M+H) ;
HPLC-Method E, R_t 1.135 min.

15 Example 397 (1H-Indazol-3-yl)-(6-methoxymethyl-2-phenyl-
pyrimidin-4-yl)-amine (IV-28) : ¹H NMR (500 MHz, DMSO) δ
3.57 (3H, s), 4.65 (2H, s), 7.23 (1H, J=7.5 Hz, t), 7.52
(1H, J=7.6 Hz, t), 7.63 (4H, m), 7.75 (1H, br), 8.13 (1H,
J=5.5 Hz, br d), 8.44 (1H, J=5.7 Hz, br d), 10.6 (1H,
br), 12.8 (1H, br s) ppm; HPLC-Method A, R_t 2.944 min; MS
(FIA) 332.1 (M+H)⁺.

20 Example 398 (5-Methyl-2H-pyrazol-3-yl)-(2-pyridin-4-yl-
thieno[3,2-d]pyrimidin-4-yl)-amine (IV-29) : ¹H NMR (DMSO)
δ 2.34 (3H, s), 6.66 (1H, s), 7.53 (1H, d), 7.84 (1H, d),
8.32 (2H, d), 8.70 (2H, d); MS 309.6 (M+H)⁺.

25 Example 399 (5-Methyl-2H-pyrazol-3-yl)-(2-phenyl-
pyrido[3,4-d]pyrimidin-4-yl)-amine (IV-30) : mp 225°C; ¹H
NMR (DMSO) δ 2.35 (3H, s), 6.81 (1H, s), 7.50-7.63 (3H,
m), 8.45-8.52 (2H, m), 8.54 (1H, d), 8.62 (1H, d), 9.20
30 (1H, s), 10.79 (1H, s), 12.38 (1H, br s); IR (solid)
2958, 2917, 2852, 1593, 1565, 1524, 1467, 1450; MS 303.2
(M+H)⁺.

Example 400 (5-Methyl-2H-pyrazol-3-yl)-(2-phenyl-pyrido[2,3-d]pyrimidin-4-yl)-amine (IV-31):
To a solution of 4-chloro-2-phenyl-pyrido[2,3-d]pyrimidine (J. Pharm. Belg., 29, 1974, 145-148) (109mg, 0.45 mmol) in THF (15 mL) was added 3-amino-5-methyl pyrazole (48 mg, 0.5 mmol) and the resulting mixture heated at 65 °C overnight. The mixture was cooled to room temperature and the resulting suspension was filtered and washed with Et₂O. The solid was dissolved in a mixture EtOH:water and the pH adjusted to pH 7. The aqueous was extracted twice with ethyl acetate and the combined organic layers were dried (MgSO₄), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO₂, DCM-MeOH gradient) to afford IV-31 as an off-white solid (69 mg, 50%): mp 234°C; ¹H NMR (DMSO) δ 2.14 (3H, s), 5.99 (1H, s), 7.20-7.40 (3H, m), 7.40-7.50 (3H, m), 8.60 (1H, d), 8.79 (1H, d), 12.82 (1H, br s); IR (solid) 2957, 2921, 2857, 1644, 1560, 1459, 1427; MS 303.2 (M+H)⁺.

20

Example 401 (5-Cyclopropyl-2H-pyrazol-3-yl)-(2-phenyl-pyrido[3,4-d]pyrimidin-4-yl)-amine (IV-32): off-white solid, mp 232-233°C; ¹H NMR (DMSO) δ 0.70-0.85 (2H, m), 0.90-1.05 (2H, m), 1.05-2.07 (1H, m), 6.75 (1H, s), 7.50-7.75 (3H, m), 8.40-8.70 (4H, m), 9.20 (1H, s), 10.80 (1H, s), 12.41 (1H); IR (solid) 3178, 1601, 1573, 1532, 1484, 1452, 1409, 1367, 1328, 802, 781, 667; MS 329.2 (M+H)⁺.

Example 402 [2-(4-Methylpiperidin-1-yl)-purin-4-yl]-(5-methyl-2H-pyrazol-3-yl)-amine (IV-33): To a suspension of 2,4-dichloro-purine (2.0 g, 10.6 mmol) in anhydrous ethanol (10 mL) was added 5-methyl-1H-pyrazol-3-yl amine (2.05 g, 21.2 mmol). The resulting mixture was stirred

at room temperature for 48 h. The resulting precipitate was collected by filtration, washed with ethanol, and dried under vacuum to afford 1.524 g (58% yield) of (2-chloro-purin-4-yl)-(5-methyl-1*H*-pyrazol-3-yl)-amine which 5 was used in the next step without further purification. To a solution of (2-chloro-purin-4-yl)-(5-methyl-1*H*-pyrazol-3-yl)-amine (200 mg, 0.80 mmol) was added 4-methylpiperidine (4 mL, 8.01 mmol) and the reaction mixture heated at reflux overnight. The solvent was 10 evaporated and the residue dissolved in a mixture EtOH:water (1:3, 4 mL). Potassium carbonate (57mg, 0.41 mmol) was added and the mixture was stirred at room temperature for 2 hours. The resulting suspension was filtered, washed with water (x2) and rinsed with Et₂O (x2) 15 to afford IV-33 as a white solid (225mg, 90%): mp >300°C; ¹H NMR (DMSO) δ 0.91 (3H, d), 1.10 (2H, m), 1.65 (3H, m), 2.24 (3H, s), 2.84 (2H, m), 4.60 (2H, m), 6.40 (1H, s), 7.87 (1H, m), 9.37-9.59 (1H, m), 12.03-12.39 (2H, m); IR (solid) 1651, 1612, 1574, 1484, 1446, 1327, 1317, 1255, 20 1203; MS 313.3 (M+H)⁺.

Example 403 (5-Cyclopropyl-2*H*-pyrazol-3-yl)-[2-(4-methylpiperidin-1-yl)-pyrrolo[3,2-d]pyrimidin-4-yl]-amine (IV-34): white solid; ¹H NMR (DMSO) δ 0.65 (2H, m), 0.91-25 0.96 (5H, m), 1.08 (2H, m), 1.58-1.64 (3H, m), 1.89 (1H, m), 2.77 (2H, t), 4.57 (2H, d), 6.09 (1H, s), 6.38 (1H, s), 7.33 (1H, s), 9.42 (1H, s), 10.65 (1H, s), 12.02 (1H, br s); MS 338.3 (M+H)⁺.

30 Example 404 [6-Benzyl-2-phenyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yl)-(5-fluoro-1*H*-indazol-3-yl)-amine (IV-35): ¹H NMR (500 MHz, DMSO-d6) δ 13.0 (s, 1H), 10.4 (s, br, 1H), 9.73 (s, 1H, TFA-OH), 8.00 (d, 2H),

7.64 (m, 2H), 7.59 (dd, 1H), 7.52 (m, 3H), 7.41 (t, 1H),
7.31 (m, 3H), 7.14 (dd, 1H), 4.58 (s, 2H), 4.35 (br, 2H),
3.74 (m, 2H), 3.17 (s, 2H) ppm. MS (ES+): m/e= 451.30
(M+H); HPLC-Method A, T_{ret} 2.96 min.

5

Example 405 (5-Fluoro-1*H*-indazol-3-yl)- (2-phenyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yl)-amine (IV-36):
Prepared from IV-35 (0.13 mmol) by treatment with an equal weight of Pd/C (10%) in 4.4% HCOOH in MeOH at room temperature for 12 h. The mixture was filtered through celite, the filtrate was evaporated, and crude product was purified by HPLC to afford IV-36 as yellow solid in 35% yield. ¹H NMR (500 MHz, DMSO-d6) δ 12.9 (s, 1H), 9.06 (s, 1H), 7.99 (d, 2H), 7.57 (dd, 1H), 7.34 (m, 1H), 7.28 (m, 3H), 7.22 (d, 1H), 3.83 (s, 2H), 3.05 (m, 2H), 2.72 (m, 2H) ppm. MS (ES+): m/e= 361.20 (M+H); HPLC-Method A, T_{ret} 2.68 min.

Example 406 (5-Methyl-2*H*-pyrazol-3-yl)- (3-phenylisoquinolin-1-yl)-amine (V-1): To a solution of 1-chloro-3-phenylisoquinoline (J. Het. Chem., 20, 1983, 121-128) (0.33g, 1.37 mmol) in DMF (anhydrous, 5 mL) was added 3-amino-5-methylpyrazole (0.27g, 2.74 mmol) and potassium carbonate (0.57g, 4.13 mmol) and the resulting mixture was heated at reflux for 6 hours. The reaction mixture was then cooled and solvent removed *in vacuo*. The residue was extracted twice with ethyl acetate and the combined organic layers washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2 , gradient DCM-MeOH) to afford V-1 as a colourless oil; ¹H NMR (MeOD) δ 2.23 (3H, s), 5.61 (1H, s), 7.41 (1H, m), 7.52 (2H, m),

7.62 (1H, m), 7.81 (1H, m), 8.07 (1H, d), 8.19 (2H, m),
8.29 (1H, s), 8.54 (1H, d); MS 301.2 (M+H)⁺.

Example 407 (1H-Indazol-3-yl)-[3-(2-trifluoromethyl-phenyl)-isoquinoline-1-yl]-amine (V-2): A solution of 1-chloro-3-(2-trifluoromethyl-phenyl)-isoquinoline (100 mg, 0.326 mmol) and 1H-indazol-3-ylamine (86 mg, 0.651 mmol) in ethanol (3 mL) was heated at 160 C and the solvent evaporated with a stream of nitrogen. The remaining oil was then heated at 160 C for 18 hours under nitrogen.

The resulting melt was dissolved in 5% methanol:dichloromethane (50 mL), washed with saturated aqueous sodium bicarbonate (1 x 25 mL) then dried over magnesium sulfate. Purification by silica gel chromatography (25% to 50% hexane:ethyl acetate) afforded V-2 as a yellow solid (35 mg, 27%). ¹H NMR (500 MHz, d₆-DMSO) δ 9.78 (br s, 1H), 8.62 (d, 1H), 7.9-7.85 (m, 1H), 7.78-7.72 (m, 1H), 7.70-7.68 (m, 1H), 7.65-7.62 (m, 1H), 7.60-7.55 (m, 1H), 7.52-7.45 (m, 3H), 7.41-7.38 (m, 1H), 7.28-7.25 (m, 1H), 7.18 (s, 1H), 6.95-6.92 (m, 1H), 5.76 (s, 1H); LC-MS (ES+) m/e= 405.18 (M+H); HPLC-Method D R_t 2.74 min.

Example 408 (5,7-Difluoro-1H-indazol-3-yl)-[3-(2-trifluoromethyl-phenyl)-isoquinolin-1-yl]-amine (V-3): Prepared from 5,7-difluoro-1H-indazol-3-ylamineto afford compound V-3 as a yellow solid (90 mg, 63%). ¹H NMR (500 MHz, d₆-DMSO) δ 13.25 (s, 1H), 9.92 (br s, 1H), 8.61 (d, 1H), 7.9 (d, 1H), 7.81-7.49 (m, 6H), 7.26-7.2 (m, 2H), 7.12-7.10 (m, 1H); LC-MS (ES+) m/e= 441.16 (M+H); HPLC-Method D, R_t 3.58 min.

Example 409 (5-Methyl-2H-pyrazol-3-yl)- (2-phenyl-quinolin-4-yl)-amine (V-4): To a mixture of 4-chloro-2-phenylquinoline (J. Het. Chem., 20, 1983, 121-128) (0.53g, 2.21 mmol) in diphenylether (5 mL) was added 3-amino-5-methylpyrazole (0.43g, 4.42 mmol) and the resulting mixture heated at 200°C overnight with stirring. The reaction mixture was cooled to ambient temperature then petroleum ether (20 mL) was added and the resulting precipitate was isolated by filtration. The crude solid was purified by flash chromatography (SiO₂, gradient DCM-MeOH) to afford V-4 as a white solid: mp 242-244°C; ¹H NMR (DMSO) δ 2.27(3H, s), 6.02(1H, s), 7.47(2H, d), 7.53-7.40(2H, br m), 7.67(1H, m), 7.92(1H, m), 8.09(2H, d), 8.48(2H, m), 9.20(1H, s), 12.17(1H, br s); IR (solid) 1584, 1559, 1554, 1483, 1447, 1430, 1389; MS 301.2 (M+H)⁺.

Example 410 (1H-Indazol-3-yl)- (2-phenyl-quinolin-4-yl)-amine (V-5): ¹H NMR (500 MHz, d₆-DMSO) δ 12.78 (s, 1H), 9.50 (s, 1H), 8.65 (d, 1H), 8.15 (s, 1H), 8.04-7.98 (m, 3H), 7.94 (s, 1H), 7.78-7.75 (m, 1H), 7.60-7.40 (m, 6H), 7.15-7.10 (m, 1H). LC-MS (ES+) m/e= 337.11 (M+H); HPLC-Method D, R_t 2.10 min.

Example 411 (2-Phenyl-quinolin-4-yl)- (1H-pyrazolo[4,3-b]pyridin-3-yl)-amine (V-6): ¹H NMR (500 MHz, DMSO-d6) δ 13.6 (s, 1H), 11.4 (s, 1H), 8.94 (d, 1H), 8.61 (dd, 1H), 8.23 (d, 1H), 8.16 (dd, 1H), 8.12 (t, 1H), 7.89 (t, 1H), 7.86 (d, 1H), 7.65 (m, 4H), 7.54 (s, 1H), 7.52 (dd, 1H) ppm. MS (ES+): m/e= 338.11 (M+H); HPLC-Method A, HPLC-Method D, R_t 2.91 min.

Example 412 (1H-Indazol-3-yl)- [2-(2-trifluoromethyl-phenyl)-quinolin-4-yl]-amine (V-7): ¹H NMR (500 MHz, d₆-

DMSO) δ 12.68 (s, 1H), 9.51 (s, 1H), 8.7 (d, 1H), 7.95-7.89 (m, 2H), 7.83-7.70 (m, 3H), 7.68-7.62 (m, 2H), 7.60 (s, 1H), 7.55-7.52 (m, 1H), 7.49-7.45 (m, 1H), 7.40-7.37 (m, 1H), 7.12-7.09 (m, 1H); LC-MS (ES+) m/e= 405.15
5 (M+H); HPLC-Method D R_t 2.25 min.

Example 413 (5,7-Difluoro-1*H*-indazol-3-yl)-[2-(2-trifluoromethyl-phenyl)-quinolin-4-yl]-amine (V-8): ¹H NMR (500 MHz, d₆-DMSO) δ 13.31 (s, 1H), 9.49 (s, 1H), 8.70-8.67 (m, 1H), 7.96-7.92 (m, 1H), 7.85-7.66 (m, 7H), 7.63-7.60 (m, 1H), 7.42-7.40 (m, 1H). LC-MS (ES+) m/e= 441.18 (M+H); HPLC-Method D R_t 2.39 min.
10

Example 414 [2-(2-trifluoromethyl-phenyl)-quinolin-4-yl]-
15 (1*H*-pyrazolo[4,3-b]pyridin-3-yl)-amine (V-9): ¹H NMR (500 MHz, DMSO-d₆) δ 13.6 (s, 1H), 11.6 (s, br, 1H), 8.98 (d, 1H), 8.57 (dd, 1H), 8.12 (m, 3H), 7.97 (m, 2H), 7.86 (m, 3H), 7.49 (dd, 1H), 7.23 (s, 1H) ppm. MS (ES+): m/e= 406.20 (M+H); HPLC-Method A R_t 2.91 min.
20

Example 415 (2-Phenyl-quinazolin-4-yl)-(2*H*-[1,2,4]triazol-3-yl)-amine (IX-154): off-white solid, mp 266-267°C; ¹H NMR (DMSO) δ 7.50-7.70 (4H, m), 7.85-8.00 (2H, m), 8.15-8.25 (2H, m), 8.37-8.45 (2H, m), 8.58 (1H, d), 13.90 (1H, br s); IR (solid) 3344, 3059, 1630, 1609, 25 1570, 1557, 1543, 1501, 1495, 1445, 1411, 1355, 1326, 1267, 1182, 1053, 1038, 760, 676, 667, 654; MS 289.2 (M+H)⁺.

30 Example 416 (5-Methyl-2*H*-[1,2,4]triazol-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (IX-155): ¹H NMR (500 MHz, DMSO-d₆) δ 8.59 (s, 1H), 8.42 (d, J = 6.7 Hz, 2H), 7.79 (m,

4H), 8.03 (m, 2H), 7.74 (m, 4H), 2.51 (s, 3H) ppm. MS (ES+): m/e= 303.08 (M+H); HPLC-Method A, R_t 2.64 min.

Example 417 (2H-[1,2,4]-Triazol-3-yl)-[2-(2-

5 trifluoromethylphenyl)-quinazolin-4-yl]-amine (IX-47):

Pale yellow solid (52% yield). ¹H NMR (500 MHz, DMSO-d6) δ 8.54 (s, 1H), 8.15 (s, br, 1H), 7.91 (t, 1H), 7.85 (m, 2H), 7.76 (m, 3H), 7.66 (t, 1H) ppm. MS (ES+): m/e= 357.13 (M+H); (ES-): m/e= 355.15 (M-H); HPLC-Method A, R_t 10 2.81 min.

Example 418 (5-Methyl-2H-[1,2,4]triazol-3-yl)-[2-(2-

trifluoromethylphenyl)-quinazolin-4-yl]-amine (IX-38):

Pale yellow solid (54% yield). ¹H NMR (500 MHz, DMSO-d6) 15 δ 8.44 (s, br, 1H), 7.92 (m, 3H), 7.84 (m, 1H), 7.77 (m, 2H), 7.68 (t, 1H), 2.28 (s, 3H) ppm. MS (ES+): m/e= 371.14 (M+H); (ES-): m/e= 369.18 (M-H); HPLC-Method A, R_t 2.89 min.

20 Example 419 (5-Methylsulfanyl-2H-[1,2,4]triazol-3-yl)-[2-(2-

trifluoromethylphenyl)-quinazolin-4-yl]-amine (IX-156):

Pale yellow solid (65% yield). ¹H NMR (500 MHz, DMSO-d6) δ 8.56 (br, 1H), 7.90 (t, 1H), 7.84 (m, 2H), 7.78 (m, 2H), 7.67 (m, 2H), 2.51 (s, 3H, buried by DMSO) ppm. 25 MS (ES+): m/e= 403.12 (M+H); (ES-): m/e= 401.16 (M-H); HPLC-Method A, R_t 3.20 min.

Example 420 (1H-[1,2,4]Triazol-3-yl)-[3-(2-

trifluoromethyl-phenyl)-isoquinolin-1-yl]-amine (IX-175):

30 A solution of 1-chloro-3-(2-trifluoromethyl-phenyl)-isoquinoline (0.326 mmol) and 1H-[1,2,4]triazol-3-ylamine (0.651 mmol) in ethanol (3 mL) was heated at 160°C and the solvent evaporated with a stream of nitrogen. The

remaining oil was then heated at 160°C for 18 hours under nitrogen. The resulting melt was dissolved in 5% methanol/dichloromethane (50 mL), washed with saturated aqueous sodium bicarbonate (1 x 25 mL) then dried over magnesium sulfate. Purification by silica gel chromatography afforded IX-175 as a colorless oil (4% yield). ^1H NMR (500 MHz, CDCl₃) δ 9.18 (d, 1H), 8.82 (s, 1H), 7.90 (d, 1H), 7.85-7.75 (m, 3H), 7.71-7.62 (m, 3H), 7.60-7.55 (m, 2H), 4.42-4.35 (m, 1H). LC-MS (ES+) 356.16 (M+H); HPLC-Method D, R_t 3.55 min.

Example 421 (2-Phenyl-quinolin-4-yl)-[1H-[1,2,4]triazol-3-yl]-amine (IX-176): Pale yellow solid (30% yield). ^1H NMR (500 MHz, d₆-DMSO) δ 13.82 (s, 1H), 9.91 (s, 1H), 8.80 (s, 1H), 8.70-8.65 (m, 1H), 8.55 (s, 1H), 8.15-8.12 (m, 2H), 8.03-7.98 (m, 1H), 7.75-7.72 (m, 1H), 7.57-7.49 (m, 3H). LC-MS (ES+) m/e= 288.11 (M+H); HPLC-Method D, R_t 1.55 min.

Example 422 [1H-[1,2,4]triazol-3-yl]-[2-(2-trifluoromethyl-phenyl)-quinolin-4-yl]-amine (IX-177): Pale yellow solid (46% yield). ^1H NMR (500 MHz, d₆-DMSO) δ 13.70 (s, 1H), 9.98 (s, 1H), 8.70 (d, 1H), 8.49 (s, 1H), 8.30 (s, 1H), 7.94-7.88 (m, 2H), 7.80-7.68 (m, 3H), 7.64-7.56 (m, 2H). LC-MS (ES+) m/e= 356.18 (M+H); HPLC-Method D, R_t 1.68 min.

Example 423 [1-H-Indazol-3-yl]-[5-methyl-6-morpholin-4-yl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine (II-251): Colorless film; 2 % yield; $^1\text{H-NMR}$ (500 MHz, CD₃OD) δ 7.84 (m, 2H), 7.71 (m, 3H), 7.41 (t, 2H), 7.14 (m, 1H), 3.74 (m, 4H), 3.69 (m, 4H), 1.24 (s, 3H) ppm; HPLC-Method A R_t 3.26 min; MS (FIA) 455.1 (M+H).

BIOLOGICAL TESTING

The activity of the compounds as protein kinase inhibitors may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of the activated protein kinase. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to the protein kinase. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/protein kinase complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with the protein kinase bound to known radioligands.

BIOLOGICAL TESTING EXAMPLE 1K_i DETERMINATION FOR THE INHIBITION OF GSK-3

Compounds were screened for their ability to inhibit GSK-3 β (AA 1-420) activity using a standard coupled enzyme system (Fox et al. (1998) *Protein Sci.* 7, 2249). Reactions were carried out in a solution containing 100 mM HEPES (pH 7.5), 10 mM MgCl₂, 25 mM NaCl, 300 μ M NADH, 1 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay were 20 μ M ATP (Sigma Chemicals, St Louis, MO) and 300 μ M peptide (HSSPHQS(PO₃H₂)EDEEE, American Peptide, Sunnyvale, CA). Reactions were carried out at 30 °C and 20 nM GSK-3 β . Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 300 μ M NADH, 30 μ g/ml pyruvate kinase and 10 μ g/ml lactate dehydrogenase.

An assay stock buffer solution was prepared containing all of the reagents listed above with the exception of ATP and the test compound of interest. The assay stock buffer solution (175 μ l) was incubated in a 5 96 well plate with 5 μ l of the test compound of interest at final concentrations spanning 0.002 μ M to 30 μ M at 30 °C for 10 min. Typically, a 12 point titration was conducted by preparing serial dilutions (from 10 mM compound stocks) with DMSO of the test compounds in 10 daughter plates. The reaction was initiated by the addition of 20 μ l of ATP (final concentration 20 μ M). Rates of reaction were obtained using a Molecular Devices Spectramax plate reader (Sunnyvale, CA) over 10 min at 30 °C. The K_i values were determined from the rate data as a 15 function of inhibitor concentration.

The following compounds were shown to have K_i values less than 0.1 μ M for GSK-3: compounds II-1, II-105, II-33, II-34, II-36, II-39, II-38, II-39, II-40, II-41, II-42, II-46, II-57, II-59, II-60, II-61, II-62, II-63, II-64, II-66, II-67, II-69, II-70, II-53, II-71, II-99, II-73, II-74, II-75, II-76, II-77, II-7, II-8, II-9, II-10, II-24, II-19, II-78, II-54, II-79, II-80, II-81, II-82, II-83, II-84, II-56, II-86, II-20, II-25, II-26, II-85, II-21, II-27, II-28, II-87, II-88, II-29, II-11, 25 II-12, II-30, II-31, II-13, II-14, II-15, II-16, II-17, II-18, II-79, II-23, II-2, II-90, II-91, II-92, II-93, II-3, II-4, II-5, II-6, II-94, II-95, II-96, II-107, II-108, II-109, II-110, II-124, II-125, II-111, II-112, II-113, II-114, II-115, II-116, II-117, II-118, II-119, II-30 120, II-121, II-208, III-8, III-7, III-9, III-37, III-38, III-39, III-40, III-42, III-45, III-46, III-47, III-48, III-49, III-51, III-52, III-53, III-54, III-55, III-56, III-57, III-58, III-59, III-60, III-61, III-62, III-63,

III-30, III-65, III-66, III-67, III-70, III-73, III-31,
III-75, III-76, III-77, III-33, III-34, III-106, III-108,
III-109, III-111, III-35, III-116, III-117, III-118, III-
119, III-120, III-121, III-127, III-128, III-141, III-
130, III-131, IV-15, IV-16, IV-17, IV-20, IV-25, IV-26,
IV-30, IV-34, V-3, and IX-47.

The following compounds were shown to have K_i values between 0.1 and 1.0 μM for GSK-3: compounds II-103, II-104, II-35, II-44, II-45, II-49, II-50, II-97, II-101, II-22, II-32, III-41, III-43, III-44, III-28, III-50, III-29, III-64, III-71, III-74, III-78, III-82, III-88, III-90, III-102, III-105, III-107, III-110, III-112, III-114, III-115, III-122, III-124, III-124, IV-1, III-1, III-138, III-140, III-142, III-129, III-132, III-134, III-135, III-136, IV-1, IV-10, IV-11, IV-12, IV-13, IV-14, IV-19, IV-21, IV-22, IV-23, IV-24, IV-3, IV-4, IV-6, IV-7, IV-8, IV-29, IV-31, IV-32, IV-33, IV-36, V-2, V-7, IX-38, IX-154, and IX-177.

The following compounds were shown to have K_i values between 1.0 and 20 μM for GSK-3: compounds II-43, II-65, II-48, II-47, II-51, II-68, II-52, II-72, II-100, II-98, II-89, III-68, III-81, III-83, III-91, III-94, III-95, III-96, III-97, III-98, III-99, III-100, III-101, III-103, III-123, III-137, III-139, III-143, III-145, III-146, V-4, V-8, IX-156, and IX-176.

BIOLOGICAL TESTING EXAMPLE 2

K_i DETERMINATION FOR THE INHIBITION OF AURORA-2

Compounds were screened in the following manner for their ability to inhibit Aurora-2 using a standard coupled enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249).

To an assay stock buffer solution containing 0.1M HEPES 7.5, 10 mM MgCl₂, 1 mM DTT, 25 mM NaCl, 2.5 mM phosphoenolpyruvate, 300 mM NADH, 30 mg/ml pyruvate kinase, 10 mg/ml lactate dehydrogenase, 40 mM ATP, and 5 800 μM peptide (LRRASLG, American Peptide, Sunnyvale, CA) was added a DMSO solution of a compound of the present invention to a final concentration of 30 μM. The resulting mixture was incubated at 30 °C for 10 min. The reaction was initiated by the addition of 10 μL of 10 Aurora-2 stock solution to give a final concentration of 70 nM in the assay. The rates of reaction were obtained by monitoring absorbance at 340 nm over a 5 minute read time at 30 °C using a BioRad Ultramark plate reader (Hercules, CA). The K_i values were determined from the 15 rate data as a function of inhibitor concentration.

The following compounds were shown to have K_i values less than 0.1 μM for Aurora-2: compounds II-33, II-34, II-36, II-37, II-40, II-41, II-55, III-7, III-9, III-37, III-38, III-39, III-40, III-41, III-42, III-44, 20 III-45, III-46, III-47, III-48, III-49, III-50, III-51, III-52, III-53, III-54, III-55, III-56, III-57, III-59, III-60, III-61, III-63, III-30, III-65, III-66, III-67, III-70, III-31, III-76, III-77, III-78, III-80, III-32, III-33, III-34, III-106, III-108, III-109, III-110, III- 25 III-111, III-112, III-114, III-35, III-115, III-116, III-117, III-118, III-119, III-120, III-121, IV-7, IV-30, IV-32, and IV-34.

The following compounds were shown to have K_i values between 0.1 and 1.0 μM for Aurora-2: compounds II- 30 1, II-105, II-35, II-38, II-39, II-42, II-64, II-70, II-53, II-99, II-77, II-79, II-86, II-20, II-93, II-94, III-28, III-58, III-64, III-71, III-73, III-74, III-75, III-

102, III-105, III-107, III-113, III-124, III-1, III-130, IV-1, IV-3, IV-4, IV-6, IV-29, IV-33, and V-4.

The following compounds were shown to have K_i values between 1.0 and 20 μM for Aurora-2: compounds II-5 103, II-104, II-57, II-59, II-61, II-63, II-67, II-69, II-75, II-76, II-10, II-19, II-78, II-54, II-80, II-82, II-21, II-90, II-91, II-96, II-107, III-68, III-79, III-82, III-101, III-103, III-127, III-141, III-129, III-132, IV-31, V-2, IX-47, IX-154, and IX-177.

10

BIOLOGICAL TESTING EXAMPLE 3

CDK-2 INHIBITION ASSAY

Compounds were screened in the following manner for their ability to inhibit CDK-2 using a standard 15 coupled enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249).

To an assay stock buffer solution containing 0.1M HEPES 7.5, 10 mM MgCl₂, 1 mM DTT, 25 mM NaCl, 2.5 mM phosphoenolpyruvate, 300 mM NADH, 30 mg/ml pyruvate 20 kinase, 10 mg/ml lactate dehydrogenase, 100 mM ATP, and 100 μM peptide (MAHHHRSPRKRAKKK, American Peptide, Sunnyvale, CA) was added a DMSO solution of a compound of the present invention to a final concentration of 30 μM . The resulting mixture was incubated at 30 °C for 10 min.

25 The reaction was initiated by the addition of 10 μL of CDK-2/Cyclin A stock solution to give a final concentration of 25 nM in the assay. The rates of reaction were obtained by monitoring absorbance at 340 nm over a 5-minute read time at 30 °C using a BioRad 30 Ultramark plate reader (Hercules, CA). The K_i values were determined from the rate data as a function of inhibitor concentration.

BIOLOGICAL TESTING EXAMPLE 4ERK INHIBITION ASSAY

Compounds were assayed for the inhibition of ERK2 by a spectrophotometric coupled-enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249). In this assay, a fixed concentration of activated ERK2 (10 nM) was incubated with various concentrations of the compound in DMSO (2.5 %) for 10 min. at 30°C in 0.1 M HEPES buffer, pH 7.5, containing 10 mM MgCl₂, 2.5 mM phosphoenolpyruvate, 200 μM NADH, 150 μg/mL pyruvate kinase, 50 μg/mL lactate dehydrogenase, and 200 μM erktide peptide. The reaction was initiated by the addition of 65 μM ATP. The rate of decrease of absorbance at 340 nm was monitored. The IC₅₀ was evaluated from the rate data as a function of inhibitor concentration.

The following compounds were shown to have a K_i value of <1μM for ERK-2: III-109, III-111, III-115, III-117, III-118, III-120, and IV-4.

The following compounds were shown to have a K_i value of between 1μM and 12μM for ERK-2: III-63, III-40, and III-108.

BIOLOGICAL TESTING EXAMPLE 5AKT INHIBITION ASSAY

Compounds were screened for their ability to inhibit AKT using a standard coupled enzyme assay (Fox et al., *Protein Sci.*, (1998) 7, 2249). Assays were carried out in a mixture of 100 mM HEPES 7.5, 10 mM MgCl₂, 25 mM NaCl , 1 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay were 170 μM ATP (Sigma Chemicals) and 200 μM peptide (RPRAATF, American Peptide, Sunnyvale, CA). Assays were carried out at 30 °C and 45 nM AKT. Final concentrations of the components of the

coupled enzyme system were 2.5 mM phosphoenolpyruvate, 300 μ M NADH, 30 μ g/ML pyruvate kinase and 10 μ g/ml lactate dehydrogenase.

An assay stock buffer solution was prepared
5 containing all of the reagents listed above, with the exception of AKT, DTT, and the test compound of interest.
56 μ l of the stock solution was placed in a 384 well plate followed by addition of 1 μ l of 2 mM DMSO stock containing the test compound (final compound
10 concentration 30 μ M). The plate was preincubated for about 10 minutes at 30 C and the reaction initiated by addition of 10 μ l of enzyme (final concentration 45 nM) and 1 mM DTT. Rates of reaction were obtained using a BioRad Ultramark plate reader (Hercules, CA) over a 5 minute read time at 30 C. Compounds showing greater than 15 50% inhibition versus standard wells containing the assay mixture and DMSO without test compound were titrated to determine IC₅₀ values.

BIOLOGICAL TESTING EXAMPLE 6

20

SRC INHIBITION ASSAY

The compounds were evaluated as inhibitors of human Src kinase using either a radioactivity-based assay or spectrophotometric assay.

Src Inhibition Assay A: Radioactivity-based Assay

25

The compounds were assayed as inhibitors of full length recombinant human Src kinase (from Upstate Biotechnology, cat. no. 14-117) expressed and purified from baculo viral cells. Src kinase activity was monitored by following the incorporation of ³³P from ATP into the tyrosine of a random poly Glu-Tyr polymer substrate of composition, Glu:Tyr = 4:1 (Sigma, cat. no. P-0275). The following were the final concentrations of the assay components: 0.05 M HEPES, pH 7.6, 10 mM MgCl₂, 2

mM DTT, 0.25 mg/ml BSA, 10 μ M ATP (1-2 μ Ci 33 P-ATP per reaction), 5 mg/ml poly Glu-Tyr, and 1-2 units of recombinant human Src kinase. In a typical assay, all the reaction components with the exception of ATP were pre-mixed and aliquoted into assay plate wells.

Inhibitors dissolved in DMSO were added to the wells to give a final DMSO concentration of 2.5%. The assay plate was incubated at 30 °C for 10 min before initiating the reaction with 33 P-ATP. After 20 min of reaction, the reactions were quenched with 150 μ l of 10% trichloroacetic acid (TCA) containing 20 mM Na₃PO₄. The quenched samples were then transferred to a 96-well filter plate (Whatman, UNI-Filter GF/F Glass Fiber Filter, cat no. 7700-3310) installed on a filter plate vacuum manifold. Filter plates were washed four times with 10% TCA containing 20 mM Na₃PO₄ and then 4 times with methanol. 200 μ l of scintillation fluid was then added to each well. The plates were sealed and the amount of radioactivity associated with the filters was quantified on a TopCount scintillation counter. The radioactivity incorporated was plotted as a function of the inhibitor concentration. The data was fitted to a competitive inhibition kinetics model to get the K_i for the compound.

25 Src Inhibition Assay B: Spectrophotometric Assay

The ADP produced from ATP by the human recombinant Src kinase-catalyzed phosphorylation of poly Glu-Tyr substrate was quantified using a coupled enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249). In this assay one molecule of NADH is oxidised to NAD for every molecule of ADP produced in the kinase reaction. The disappearance of NADH can be conveniently followed at 340 nm.

The following were the final concentrations of the assay components: 0.025 M HEPES, pH 7.6, 10 mM MgCl₂, 2 mM DTT, 0.25 mg/ml poly Glu-Tyr, and 25 nM of recombinant human Src kinase. Final concentrations of the 5 components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 200 μM NADH, 30 μg/ml pyruvate kinase and 10 μg/ml lactate dehydrogenase.

In a typical assay, all the reaction components with the exception of ATP were pre-mixed and aliquoted 10 into assay plate wells. Inhibitors dissolved in DMSO were added to the wells to give a final DMSO concentration of 2.5%. The assay plate was incubated at 30 C for 10 min before initiating the reaction with 100 μM ATP. The 15 absorbance change at 340 nm with time, the rate of the reaction, was monitored on a molecular devices plate reader. The data of rate as a function of the inhibitor concentration was fitted to competitive inhibition kinetics model to get the K_i for the compound.

The following compounds were shown to have a K_i 20 value of <100nM on SRC: III-31, III-32, III-33, III-34, III-35, III-47, III-65, III-66, III-37, III-38, III-39, III-40, III-42, III-44, III-48, III-49, III-70, III-45, III-78, III-76, and IV- 32.

The following compounds were shown to have a K_i 25 value of between 100nM and 1μM for SRC: III-63, III-71, III-75, III-73, III-72, III-74, III-80, III-50, IV-30.

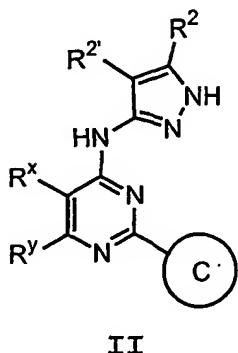
The following compounds were shown to have a K_i value of between 1μM and 6μM for SRC: III-79, IV-1, and IV-31.

30 While we have hereinbefore presented a number of embodiments of this invention, it is apparent that our basic construction can be altered to provide other embodiments which utilize the compounds and methods of

this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments which have been represented by way of example.

We claim:

1. A compound of formula II:



or a pharmaceutically acceptable derivative or prodrug thereof, wherein;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C has one or two ortho substituents independently selected from -R¹, any substitutable non-ortho carbon position on Ring C is independently substituted by -R⁵, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or -R⁸;

R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or -R⁸, said C₁₋₆ aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R¹

and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C; R^x and R^y are independently selected from T-R³, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is substituted by oxo or T-R³, and any substitutable nitrogen on said ring formed by R^x and R^y is substituted by R⁴;

T is a valence bond or a C₁₋₄ alkylidene chain;

R² and R^{2'} are independently selected from -R, -T-W-R⁶, or R² and R^{2'} are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R² and R^{2'} is substituted by halo, oxo, -CN, -NO₂, -R⁷, or -V-R⁶, and any substitutable nitrogen on said ring formed by R² and R^{2'} is substituted by R⁴;

R³ is selected from -R, -halo, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)CO₂(C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁷)₂;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R⁵ is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂, or R⁵ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

W is -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)-, or -CON(R⁶)-;

each R⁶ is independently selected from hydrogen or an optionally substituted C₁₋₄ aliphatic group, or two R⁶ groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

each R⁷ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R⁸ is independently selected from an optionally substituted C₁₋₄ aliphatic group, -OR⁶, -SR⁶, -COR⁶, -SO₂R⁶, -N(R⁶)₂, -N(R⁶)N(R⁶)₂, -CN, -NO₂, -CON(R⁶)₂, or -CO₂R⁶.

2. The compound according to claim 1, wherein said compound has one or more features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from an optionally substituted naphthyl, quinolinyl or isoquinolinyl ring;

(b) R^X is hydrogen or C₁₋₄ aliphatic and R^Y is T-R³, or R^X and R^Y are taken together with their intervening atoms to form an optionally substituted 5-7 membered unsaturated or partially unsaturated ring having 0-2 ring nitrogens;

(c) R¹ is -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶; and

(d) R² is hydrogen and R² is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C₁₋₆ aliphatic group, or R² and R² are taken together with their intervening atoms to form a

substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

3. The compound according to claim 2, wherein:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from an optionally substituted naphthyl, quinolinyl or isoquinolinyl ring;

(b) R^x is hydrogen or C₁₋₄ aliphatic and R^y is T-R³, or R^x and R^y are taken together with their intervening atoms to form an optionally substituted 5-7 membered unsaturated or partially unsaturated ring having 0-2 ring nitrogens;

(c) R¹ is -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶; and

(d) R² is hydrogen and R² is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C₁₋₆ aliphatic group, or R² and R²' are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

4. The compound according to claim 2, wherein said compound has one or more features selected from the group consisting of:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring

system, the bicyclic ring system is selected from an optionally substituted naphthyl ring;

(b) R^x is hydrogen or methyl and R^y is -R, N(R⁴)₂, or -OR, or R^x and R^y are taken together with their intervening atoms to form a 5-7 membered unsaturated or partially unsaturated carbocyclo ring optionally substituted with -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂;

(c) R¹ is -halo, a C₁₋₆ haloaliphatic group, a C₁₋₆ aliphatic group, phenyl, or -CN;

(d) R^{2'} is hydrogen and R² is hydrogen or a substituted or unsubstituted group selected from aryl, or a C₁₋₆ aliphatic group, or R² and R^{2'} are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring; and

(e) each R⁵ is independently selected from -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, and -N(R⁴)SO₂R.

5. The compound according to claim 4, wherein:

(a) Ring C is a phenyl or pyridinyl ring, optionally substituted by -R⁵, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from an optionally substituted naphthyl ring;

(b) R^x is hydrogen or methyl and R^y is -R, N(R⁴)₂, or -OR, or R^x and R^y are taken together with their

intervening atoms to form a 5-7 membered unsaturated or partially unsaturated carbocyclo ring optionally substituted with -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂ (optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂; ;

(c) R¹ is -halo, a C₁₋₆ haloaliphatic group, a C₁₋₆ aliphatic group, phenyl, or -CN;

(d) R^{2'} is hydrogen and R² is hydrogen or a substituted or unsubstituted group selected from aryl, or a C₁₋₆ aliphatic group, or R² and R^{2'} are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring; and

(e) each R⁵ is independently selected from -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -SO₂N(R⁴)₂, and -N(R⁴)SO₂R.

6. The compound according to claim 4, wherein said compound has one or more features selected from the group consisting of:

(a) R^x is hydrogen or methyl and R^y is methyl, methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or an optionally substituted group selected from 2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^x and R^y are taken together with their intervening atoms to form a 6-membered unsaturated or partially unsaturated carbocyclo ring optionally substituted with -halo, -R, -OR, -COR, -CO₂R, -CON(R⁴)₂, -CN, or -N(R⁴)₂ wherein R is an optionally substituted C₁₋₆ aliphatic group;

(b) R¹ is -halo, a C₁₋₄ aliphatic group optionally substituted with halogen, or -CN;

(c) R² and R^{2'} are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN, -SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, or -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group; and

(d) each R⁵ is independently selected from -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic).

7. The compound according to claim 6, wherein:

(a) R^x is hydrogen or methyl and R^y is methyl, methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or an optionally substituted group selected from 2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^x and R^y are taken together with their intervening atoms to form a benzo ring or a partially unsaturated carbocyclo ring optionally substituted with -halo, -R, -OR, -COR, -CO₂R, -CON(R⁴)₂, -CN, or -N(R⁴)₂ wherein R is an optionally substituted C₁₋₆ aliphatic group;

(b) R¹ is -halo, a C₁₋₄ aliphatic group optionally substituted with halogen, or -CN;

(c) R² and R^{2'} are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, -N(R⁴)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂(C₁₋₄ alkyl), -CN,

-SO₂(C₁₋₄ alkyl), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄ alkyl), -NHC(O)(C₁₋₄ alkyl), -C(O)NH₂, or -CO(C₁₋₄ alkyl), wherein the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group; and

(d) each R⁵ is independently selected from -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, and -CO₂(C₁₋₄ aliphatic).

8. The compound according to claim 7, wherein R^x and R^y are each methyl or R^x and R^y are taken together with the pyrimidine ring to form an optionally substituted ring selected from quinazoline or tetrahydroquinazoline, and R² and R^{2'} are taken together with the pyrazole ring to form an optionally substituted indazole ring.

9. The compound according to claim 1, wherein said compound is selected from Table 1.

10. A composition comprising a compound according carrier.

11. The composition according to claim 10 further comprising a second therapeutic agent.

12. A method of inhibiting GSK-3 or Aurora activity in a patient comprising the step of administering to said patient a therapeutically effective amount of the composition according to claim 10.

13. The method according to claim 12, wherein said method inhibits GSK3 activity in a patient.

14. A method of inhibiting GSK-3 or Aurora activity in a biological sample comprising contacting said biological with the compound according to claim 1.

15. A method of treating a disease that is alleviated by treatment with an GSK-3 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of the composition according to claim 10.

16. The method according to claim 15 further comprising the step of administering to said patient a second therapeutic agent.

17. The method according to claim 15, wherein said disease is diabetes.

18. The method according to claim 15, wherein said disease is Alzheimer's disease.

19. The method according to claim 15, wherein said disease is schizophrenia.

20. A method of enhancing glycogen synthesis in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically effective amount of the composition according to claim 10.

21. A method of lowering blood levels of glucose in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically

effective amount of the composition according to claim 10.

22. A method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically effective amount of the composition according to claim 10.

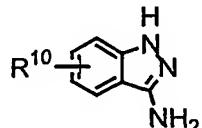
23. A method of inhibiting the phosphorylation of β -catenin in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically effective amount of the composition according to claim 10.

24. A method of treating a disease that is alleviated by treatment with an aurora inhibitor, which method comprises the step of administering to a patient in need of such a treatment a therapeutically effective amount of the composition according to claim 10.

25. The method according to claim 24, further comprising the step of administering to said patient a second therapeutic agent.

26. The method according to claim 24 wherein said disease is cancer.

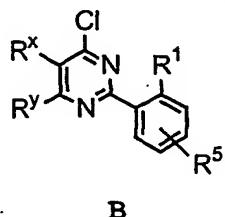
27. A compound of formula A:



A

wherein R¹⁰ is one to three substituents that are each independently selected from fluoro, bromo, C₁₋₆ haloalkyl, nitro, or 1-pyrrolyl.

28. A compound of formula B:



wherein:

R¹ is selected from Cl, F, CF₃, CN, or NO₂;

R⁵ is one to three substituents that are each independently selected from H, Cl, F, CF₃, NO₂, or CN, provided that R¹ and R⁵ are not simultaneously Cl;

R^x and R^y are independently selected from T-R³, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is optionally and independently substituted by T-R³, and any substitutable nitrogen on said ring formed by R^x and R^y is substituted by R⁴;

T is a valence bond or a C₁₋₄ alkylidene chain;

R³ is selected from -R, -halo, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)CO₂ (optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁷)₂;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10

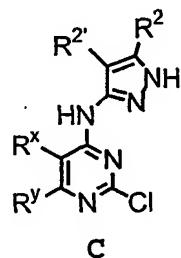
ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R⁷ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring.

29. The compound according to claim 28 wherein R¹ is CF₃.

30. A compound of formula C:



wherein:

R² and R^{2'} are independently selected from -R, -T-W-R⁶, or R² and R^{2'} are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R² and R^{2'} is substituted by halo, oxo, -CN, -NO₂, -R⁷, or -V-R⁶; and any substitutable nitrogen on said ring formed by R² and R^{2'} is substituted by R⁴;

R^x and R^y are independently selected from $T-R^3$, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is optionally and independently substituted by $T-R^3$, and any substitutable nitrogen on said ring formed by R^x and R^y is substituted by R^4 ;

T is a valence bond or a C_{1-4} alkylidene chain;

V is $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-N(R^6)SO_2-$, $-SO_2N(R^6)-$, $-N(R^6)-$, $-CO-$, $-CO_2-$, $-N(R^6)CO-$, $-N(R^6)C(O)O-$, $-N(R^6)CON(R^6)-$, $-N(R^6)SO_2N(R^6)-$, $-N(R^6)N(R^6)-$, $-C(O)N(R^6)-$, $-OC(O)N(R^6)-$, $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-C(R^6)_2N(R^6)C(O)-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, or $-C(R^6)_2N(R^6)CON(R^6)-$;

W is $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-CO-$, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)OC(O)N(R^6)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, $-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;

R^3 is selected from $-R$, $-halo$, $-OR$, $-C(=O)R$, $-CO_2R$, $-COCOR$, $-COCH_2COR$, $-NO_2$, $-CN$, $-S(O)R$, $-S(O)_2R$, $-SR$, $-N(R^4)_2$, $-CON(R^7)_2$, $-SO_2N(R^7)_2$, $-OC(=O)R$, $-N(R^7)COR$, $-N(R^7)CO_2$ (optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^7)CON(R^7)_2$, $-N(R^7)SO_2N(R^7)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^7)_2$;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10

ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring.

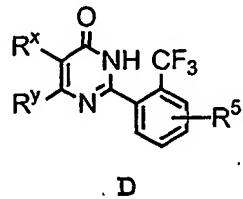
each R⁶ is independently selected from hydrogen or an optionally substituted C₁₋₄ aliphatic group, or two R⁶ groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring; and

each R⁷ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring.

31. The compound according to claim 30, wherein R^x and R^y are each methyl, or R^x and R^y are taken together with the pyrimidine ring to form a quinazoline or tetrahydroquinazoline ring.

32. The compound according to claim 31, wherein R² and R^{2'} are taken together with the pyrazole ring to form an indazole ring.

33. A compound of formula D:



wherein:

R^x and R^y are independently selected from $T-R^3$, or R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^x and R^y is optionally and independently substituted by $T-R^3$, and any substitutable nitrogen on said ring formed by is substituted by R^4 ;

T is a valence bond or a C_{1-4} alkylidene chain;

R^3 is selected from -R, -halo, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)CO₂(optionally substituted C_{1-6} aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁷)₂;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from -R⁷, -COR⁷, -CO₂(optionally substituted C_{1-6} aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R^5 is independently selected from -R, halo, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C_{1-6} aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or -OC(=O)N(R⁴)₂.

34. The compound according to claim 33, wherein R^x and R^y are each methyl, or R^x and R^y are taken together with the pyrimidine ring to form a quinazoline or tetrahydroquinazoline ring.

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 01/28940

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/12	C07D401/14	A61K31/506	A61K31/4155	A61P35/00
C07D403/14	C07D405/14	C07D409/14	C07D471/04	C07D487/04
C07D401/12	C07D493/04	C07D498/04	C07D513/04	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 21955 A (PASQUET GEORGES ; HENNEQUIN LAURENT FRANCOIS AND (FR); ZENECA PHARM) 20 April 2000 (2000-04-20) examples 16-20 ---	1,17,24, 26
A	WO 00 39101 A (BREAULT GLORIA ANNE ; PEASE JANET ELIZABETH (GB); ASTRAZENECA UK LT) 6 July 2000 (2000-07-06) example 50 example 88 ---	1,24,26
X		30
A	WO 95 15758 A (HSU CHIN YI JENNY ; ZILBERSTEIN ASHER (US); JOHNSON SUSAN E (US); M) 15 June 1995 (1995-06-15) page 15, line 22 ---	1,24,26
		-/-



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

• Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

7 January 2002

Date of mailing of the international search report

22/01/2002

Name and mailing address of the ISA

European Patent Office, P.O. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

De Jong, B

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/YUS 01/28940

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TRAXLER P ET AL: "USE OF A PHARMACOPHORE MODEL FOR THE DESIGN OF EGF-R TYROSINE KINASE INHIBITORS: 4-(PHENYLAMINO)PYRAZOLO3,4-DPYRIMIDINES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 40, no. 22, 1997, pages 3601-3616, XP001009913 ISSN: 0022-2623 page 3603 ---	1,24,26
A	WO 98 14450 A (CIBA GEIGY AG ;TRAXLER PETER (CH); BOLD GUIDO (CH); FREI JOERG (CH) 9 April 1998 (1998-04-09) claim 1; examples ---	1,24,26
X	E.W. PARRELL: "2-Cyano-4-nitrophenylhydrazine and 3-Amino-5-nitroindazole" JOURNAL OF THE CHEMICAL SOCIETY., 1959, pages 2363-2365, XP002185285 CHEMICAL SOCIETY. LETCHWORTH., GB compound (I) ---	27
X	US 3 935 183 A (BARON THOMAS DOUGLAS ET AL) 27 January 1976 (1976-01-27) column 5, line 9 ---	27
X	DE 24 58 965 A (BAYER AG) 16 June 1976 (1976-06-16) example 14 ---	27
X	US 3 133 081 A (LAFFERTY ET AL) 1964 examples 1,2,5,6 ---	27
X	M. PATRIDGE ET AL: "Cyclic Amidines." JOURNAL OF THE CHEMICAL SOCIETY. C, no. 19, 1970, pages 2641-2647, XP002185286 CHEMICAL SOCIETY. LETCHWORTH., GB compounds of formula (III) ---	28
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BAIG, GHOUSE UNISSA ET AL: "Triazines and related products. Part 27. Thermolysis of 4-anilino-1,2,3-benzotriazines" retrieved from STN Database accession no. 101:151814 XP002185287 compound with RN=91961-09-0 & J. CHEM. SOC., PERKIN TRANS. 1 (1984), (5), 999-1003 , ---	28
	-/-	

INTERNATIONAL SEARCH REPORT

In 1al Application No

PCT/US 01/28940

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MEDWID, JEFFREY B. ET AL: "Preparation of triazolo[1,5-c]pyrimidines as potential antiasthma agents" retrieved from STN Database accession no. 112:216851 XP002185288 compound with RN=125904-00-9 & J. MED. CHEM. (1990), 33(4), 1230-41 , ---	28
X	US 3 998 951 A (HARNISH WAYNE NELSON ET AL) 21 December 1976 (1976-12-21) example VI ---	28
X	US 4 493 726 A (BURDESKA KURT ET AL) 15 January 1985 (1985-01-15) compound 67 ---	28
X	WO 99 62518 A (CADUS PHARMACEUTICAL CORP ;MCKIBBEN BRYAN (US); WITTER DAVID J (US) 9 December 1999 (1999-12-09) page 66, line 1 ---	28
X	WO 93 22681 A (NEUROGEN CORP ;HUTCHISON ALAN (US); SHAW KENNETH (US); TALLMAN JOH) 11 November 1993 (1993-11-11) example X ---	28
X	US 5 972 946 A (ITOH MARI ET AL) 26 October 1999 (1999-10-26) reference examples 42,44 ---	28
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TORIYABE, KEIJI ET AL: "Preparation of sulfur-containing arylthiazoles and insecticides" retrieved from STN Database accession no. 132:93314 XP002185289 compound with RN=254995-13-6 & JP 2000 026421 A (KUMIAI CHEMICAL INDUSTRY CO., LTD., JAPAN;IHARA CHEMICAL INDUSTRY CO.,) 25 January 2000 (2000-01-25) ---	28
P,X	WO 01 60816 A (AMGEN INC) 23 August 2001 (2001-08-23) example 10 ----	30

INTERNATIONAL SEARCH REPORT

Int	Application No
PCT/US 01/28940	

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0021955	A	20-04-2000	AU BR CN EP WO NO	6112899 A 9914326 A 1322202 T 1119567 A1 0021955 A1 20011739 A	01-05-2000 26-06-2001 14-11-2001 01-08-2001 20-04-2000 07-06-2001
WO 0039101	A	06-07-2000	AU BR EP WO NO	1874300 A 9916590 A 1140860 A1 0039101 A1 20013038 A	31-07-2000 23-10-2001 10-10-2001 06-07-2000 22-08-2001
WO 9515758	A	15-06-1995	US US AU EP SG WO US US US US US US US US US	5480883 A 5710158 A 1305095 A 0871448 A1 54172 A1 9515758 A1 5795889 A 5646153 A 5721237 A 5714493 A 6057320 A RE36256 E	02-01-1996 20-01-1998 27-06-1995 21-10-1998 16-11-1998 15-06-1995 18-08-1998 08-07-1997 24-02-1998 03-02-1998 02-05-2000 20-07-1999
WO 9814450	A	09-04-1998	AU AU WO EP JP US	720135 B2 4864297 A 9814450 A1 0929553 A1 2001501216 T 6251911 B1	25-05-2000 24-04-1998 09-04-1998 21-07-1999 30-01-2001 26-06-2001
US 3935183	A	27-01-1976	BE CH DE FR GB NL	761823 A1 556892 A 2103612 A1 2077324 A5 1308917 A 7100628 A	20-07-1971 13-12-1974 25-11-1971 22-10-1971 07-03-1973 28-07-1971
DE 2458965	A	16-06-1976	DE AT AT AU BE CA CH CS DD DK ES FI FR GB HK HU IE IL	2458965 A1 343653 B 939775 A 8717075 A 836528 A1 1059523 A1 622250 A5 189731 B2 125484 A5 567275 A , B, 443429 A1 753493 A 2293928 A1 1490306 A 52580 A 173557 B 42208 B1 48642 A	16-06-1976 12-06-1978 15-10-1977 09-06-1977 11-06-1976 31-07-1979 31-03-1981 30-04-1979 20-04-1977 14-06-1976 16-04-1977 14-06-1976 09-07-1976 02-11-1977 26-09-1980 28-06-1979 18-06-1980 30-12-1979

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 01/28940

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
DE 2458965	A		JP 51082266 A KE 3078 A LU 73993 A1 NL 7514521 A NO 754024 A , B, SE 419645 B SE 7513990 A SU 604487 A3 US 4051252 A YU 315275 A1 ZA 7507777 A	19-07-1976 03-10-1980 11-11-1976 15-06-1976 15-06-1976 17-08-1981 14-06-1976 25-04-1978 27-09-1977 28-02-1982 24-11-1976
US 3133081	A		NONE	
US 3998951	A	21-12-1976	US B450870 I5	16-03-1976
US 4493726	A	15-01-1985	AT 32065 T AU 558710 B2 AU 7884081 A BG 37221 A3 BR 8108383 A CA 1220953 A1 CS 8109672 A2 DD 202798 A5 DE 3176621 D1 DK 571281 A , B, EP 0055693 A1 ES 508254 D0 ES 8300322 A1 GR 76379 A1 HU 191339 B IL 64612 A IN 159209 A1 KR 8901062 B1 LV 5152 A3 MX 6720 E NZ 199360 A OA 6972 A PH 19369 A PL 234418 A1 PT 74181 A PT 74181 B RO 83451 A1 SU 1482505 A3 US 4674229 A YU 305881 A1 ZW 30681 A1 JP 1634449 C JP 2053402 B JP 61246102 A JP 1417415 C JP 57131702 A JP 62025641 B LT 2607 R3 ZA 8108852 A	15-02-1988 05-02-1987 01-07-1982 15-04-1985 13-10-1982 28-04-1987 15-08-1985 05-10-1983 25-02-1988 24-06-1982 07-07-1982 01-11-1982 16-01-1983 06-08-1984 27-02-1987 30-09-1988 11-04-1987 22-04-1989 10-10-1993 07-11-1985 11-04-1986 31-07-1983 02-04-1986 02-08-1982 02-01-1982 04-01-1985 21-02-1984 23-05-1989 23-06-1987 30-04-1984 14-07-1982 20-01-1992 16-11-1990 01-11-1986 22-12-1987 14-08-1982 04-06-1987 25-03-1994 29-12-1982
WO 9962518	A	09-12-1999	AU 4226599 A BR 9911612 A	20-12-1999 06-02-2001

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 01/28940

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9962518	A		CN 1311680 T EP 1082120 A1 NO 20006090 A WO 9962518 A1	05-09-2001 14-03-2001 31-01-2001 09-12-1999
WO 9322681	A	11-11-1993	US 5597920 A AT 158414 T AU 691470 B2 AU 4117793 A CA 2134227 A1 DE 69314024 D1 DE 69314024 T2 DK 639275 T3 EP 0639275 A1 ES 2110090 T3 GR 3025698 T3 JP 8500333 T WO 9322681 A1 US 5688654 A	28-01-1997 15-10-1997 21-05-1998 29-11-1993 11-11-1993 23-10-1997 16-04-1998 14-04-1998 22-02-1995 01-02-1998 31-03-1998 16-01-1996 11-11-1993 18-11-1997
US 5972946	A	26-10-1999	AU 694647 B2 AU 5287496 A BR 9604894 A CA 2218033 A1 CN 1186487 A CZ 9703223 A3 EP 0826673 A1 HU 9801688 A2 IL 117659 A WO 9632383 A1 NO 974685 A NZ 304982 A PL 322819 A1 SK 137497 A3 ZA 9602438 A	23-07-1998 30-10-1996 14-07-1998 17-10-1996 01-07-1998 18-02-1998 04-03-1998 29-03-1999 06-12-2000 17-10-1996 12-12-1997 29-03-1999 16-02-1998 06-05-1998 01-10-1996
JP 2000026421	A	25-01-2000	NONE	
WO 0160816	A	23-08-2001	AU 3704101 A WO 0160816 A1	27-08-2001 23-08-2001